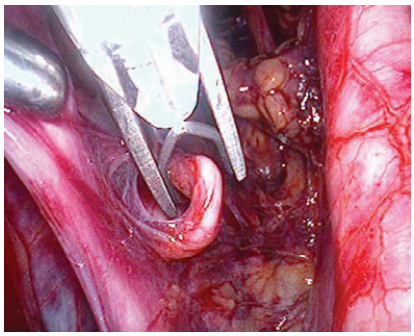
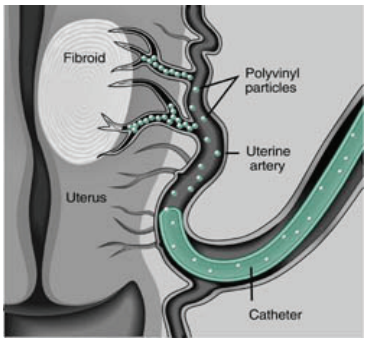
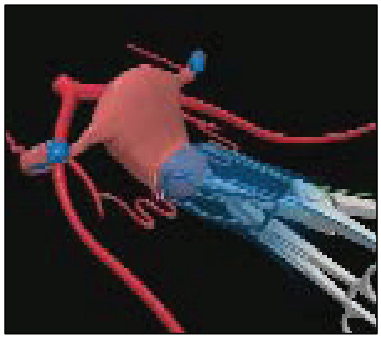
Uterine sparing treatment of leiomyomas by central or peripheral occlusion of the arterial supply







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1. LIST OF PAPERS

I. Kirsten Hald, Anton Langebrekke, Nils-Einar Kløw, Hans Jørgen Noreng, Anette Bugge Berge, Olav Istre. *Laparoscopic occlusion of uterine vessels for the treatment of symptomatic fibroids: Initial experience and comparison to uterine artery embolization.* American Journal of Obstetrics and Gynecology 2004; 190,37-43.

II. Kirsten Hald, Nils-Einar Kløw, Erik Qvigstad, Olav Istre. *Laparoscopic Occlusion Compared With Embolization of Uterine Vessels. A Randomized Controlled Trial.* Obstetrics & Gynecology 2007; 109,20-27.

III. Olav Istre, Kirsten Hald, Erik Qvigstad. *Multiple Myomas Treated with a Temporary, Noninvasive, Doppler-Directed, Transvaginal Uterine Artery Clamp.* The Journal of the American Association of Gynecologic Laparoscopists 2004; May;11(2):273-276.

IV. Kirsten Hald, Nils-Einar Kløw, Erik Qvigstad, Olav Istre. *Treatment of Uterine Myomas with Transvaginal Uterine Artery Occlusion: Possibilities and Limitations.* The Journal of Minimally Invasive Gynecology 2008; Sept- Oct;15(5):631-635.

V. Kirsten Hald, Hans Jørgen Noreng, Olav Istre, Nils-Einar Kløw. *Uterine artery embolization versus laparoscopic occlusion of uterine arteries for leiomyomas: Long term results of a randomized comparative trial.* Accepted for publication in Journal of Vascular and Interventional Radiology (JVIR).

2. ABBREVIATIONS

AMH	Anti-Müllarian Hormone
CE	Contrast Enhancement
CIRSE	Cardiovascular and Interventional Radiological Society of Europe
D&C	Dilatation and Curretage
D-UAO	Doppler-directed Uterine Artery Occlusion
DSA	Digital Substraction Angiography
FIBROID	Fibroid Registry for Outcomes Data
FSH	Follicle stimulating hormone
GnRHa	Gonadothropin Releasing Hormone analoge
Gy	Gray
LNG-IUS	Levonogestrel-releasing Intrauterine System
LUAO	Laparoscopic uterine artery occlusion
MRgFUS	Magnetic-resonance-guided high intensity focused ultrasound
MRI	Magnetic Resonance Imaging
ME	Maximum Enhancement
PACS	Picture Archiving and Communication System
PBAC	Pictorial Blood Loss Assessment Chart
PVA	Polyvinyl Alcohol
RCT	Randomized Controlled Trial
ROI	Region of Interest
SERM	Selective Estrogen Receptor Modulator
SIR	Society of Interventional Radiologists
SPRM	Selective Progesterone Receptor Modulator
TAGM	Tris-acryl Gelatin Microspheres
TCR	Transcervical Resection
TCRM	Transcervical Resection of Myomas
UAE	Uterine Artery Embolization
VAS	Visual Analog Scale

3. INTRODUCTION

In the year of 2000, the gynecological and the radiological departments at Oslo University Hospital, Ullevål (former Ullevål University Hospital) agreed to cooperate with the objective to implement two new modalities aimed to treat symptomatic uterine leiomyomas in a conservative manner; uterine artery embolization (UAE) and bilateral laparoscopic occlusion of uterine arteries (LUAO). We decided to register important preoperative and postoperative variables including outcome measurements of the first 100 patients treated. We also decided to design a randomized study to compare the two methods of treatment. In 2003, we agreed to take part in an experimental study aimed to evaluate a completely new device for treatment of uterine leiomyomas; a temporary noninvasive Doppler-directed transvaginal uterine artery clamp (D-UAO). The studies presented in this thesis consist of ninety-five of these patients.

3.1 Uterine leiomyomas

3.1.1 Prevalence, morbidity and risk-factors

Leiomyomas of the uterus is a benign tumor originating from the myometrial tissue in the uterus wall. Most commonly the tumor is located in the uterine body, but may also be found in the cervix, the broad ligament and the ovary. Leiomyomas is a major source of gynecological morbidity. The prevalence increases with age up to menopause (1). After menopause, the leiomyomas shrink (2), probably depending on decreased hormonal production. From an American study of serial sections of uteri, it has been estimated that up to 77% of women of reproductive age have leiomyomas (2). In another American study, 1364 premenopausal women were randomly selected for ultrasound screening of the uterus. The estimated cumulative incidence of leiomyomas by the age of 50 was more than 80% for African-American women and nearly 70% for Caucasians (1).
It is estimated that 20-50% of leiomyomas will cause symptoms (2,3).
Leiomyomas vary in size, number and location, and the degree of symptoms is often depending of all these factors. The most common symptom is menorrhagia, which might lead to dysmenorrhoe and anemia. Large tumors independent of location may place pressure on adjacent organs and cause bulk sensation, urinary frequency and, less frequently, pain. Sometimes the only symptom is abdominal distension with discomfort and possibly

cosmetic complains. Leiomyomas are associated with sub-fertility, increased rate of pregnancy loss and risk of obstetrical complications (4-6).
Consistently reported risk factors for leiomyoma are early menarche, nulliparity (7) and obesity (8,9). Lower risk is reported among smokers (10) and women who exercise more than 7 hours/week (11). Hormonal oral contraceptives are generally considered as relatively contraindicated in women with leiomyomas. However, the link between oral contraceptive use and leiomyomas has been inconsistently reported in different studies (12-14). The use of progestogen injections such as medroxyprogesterone acetate is reported to reduce the risk of leiomyomas (14,15). The effect of a levonogestrel-releasing intra-uterine device on the risk of developing leiomyomas is uncertain, however, studies have indicated that a reduced risk might be present (16,17). Compared with women of Caucasian, Asian and Hispanic origin, women of African origin have more commonly leiomyomas. Women of African origin also develop leiomyomas at an earlier age, have a higher frequency of multiple lesions and also greater sizes of the leiomyomas (1,18).

3.1.2 Pathophysiology

The normal myometrium consists of smooth muscle cells and fibrotic tissue. Histologically, the leiomyomas are characterized by whirling bundles of smooth muscle cells, mimicking the normal muscle bundles of the myometrium. Foci of fibrosis, calcification, ischemic necrosis and haemorrhage may also be present (19). Degenerative changes vary inside the leiomyomas. The most common form is hyaline degeneration, in which the smooth muscle cells are replaced by collagen. Red degeneration is characterized by multifocal areas of recent haemorrhage that occur in women in reproductive age either taking oral contraceptives or who are pregnant or recently postpartum. Unlike hyaline change, the microscopic appearance in red degeneration shows the ghosts of the muscle cells and their nuclei. Later, the periphery of a leiomyoma that has undergone red degeneration may become white and calcified. Calcification is typical for older leiomyomas on the whole, commonly seen after menopause. Treatment with Gonadothropin-releasing hormone analogs or uterine artery embolization leads to infarct type necrosis, secondary to ischemia. It is characterized by finding either granulation tissue or hyalinization between the necrotic and non-necrotic areas, associated with recent hemorrhage. The end result is replacement of the infarcted area by dense hyaline tissue or calcification. For the pathologist, it may be difficult, however important, to distinguish the early stages of necrosis from the tumor cell necrosis seen in the malignant leiomyosarcomas. Other benign variants of leiomyomas like

the cellular and leiomyomas with bizarre nuclei (symplastic leiomyomas) are also important to recognize, as they can be misinterpreted as sarcomas (20,21).

Immunohistochemical analyses of the leiomyoma vasculature have revealed higher microvascular density in the myometrium compared to in leiomyomas of all sizes. Vessels with a larger mean surface was found in myometrium and in large leiomyomas compared to in small leiomyomas (22). Kurjak et al. used color-Doppler ultrasound and found that the vascularity of the leiomyomas was dependent on tumor size, position and the extent of secondary degenerative changes (23). In another study, local and intra-arterial injection of 133Xe demonstrated significantly lower blood flow in the leiomyomas compared to surrounding myometrium (24,25).

The mechanism of increased menstrual bleeding in women with leiomyomas is not known. In a study using electron microscopic techniques, myometrium from uteri with leiomyomas had ultrastructural characteristics that were different from those in myometrium from uteri without leiomyomas (26). The myometrium in the leiomyomatous uterus has increased number of arterioles and venules and venule ecstasia (27). Although the venous abnormalities were originally thought to be due to physical compression of the vascular structures by bulky tumors, it is hypothesized that molecular changes leads to increased vessel numbers or abnormal function (28).

Although leiomyomas seem homogenous in their macroscopic phenotype, molecular and cytogenetic studies have demonstrated that they are heterogeneous in their natural history and etiology. Differences in the amount of hormone receptors, the degree of fibrotic tissue, vascular changes, secretion of prostaglandins from smooth muscle cells and the expression of growth factor and cytokines are some of the factors that probably are responsible for the variable ability to grow and to induce symptoms like bleeding, pressure and pain (28).

Genetics

It is believed that a genetic element is present in the development of leiomyomas. Leiomyomas appear to be two-to three-fold more common in first-degree relatives of women with leiomyomas, compared with the general population (10). Several hereditary cancer syndromes predisposing to leiomyomas suggest a genetic linkage with renal cell carcinoma (RCC) (29). These syndromes include hereditary leiomyomatosis and RCC, tuberous sclerosis complex and Birt-Hogg-Dubé syndrome. The racial differences might also indicate that genetic predisposition play a role, and twin studies have also supported a strong hereditary factor (30-32).

Cytogenetic studies have demonstrated that most leiomyomas are monoclonal in their origin (33,34). The majority is cytogenically normal, however chromosomal abnormalities are seen in about 40% of leiomyomas. Coexisting normal and abnormal karyotypes can be found in one single leiomyoma and different karyotypic abnormalities can be found in multiple leiomyomas in the same uterus (35). It is unclear if the chromosomal aberrations are primary or secondary events.

Theories of initiation

The initiation process of uterine leiomyomas is not known, although there are several theories. One hypothesis states that increased levels of estrogen and progesterone increases the mitotic rate which again increases the likelihood of somatic mutations and development of leiomyomas (36). Richards and Tiltman used immunocytochemistry to examine the myometrium from leiomyomatous uteri and compared it with myometrium from normal uteri. They found that the myometrium of uteri with leiomyomas expresses significantly increased levels of estrogen receptors compared with myometrium from the non-leiomyomatous uteri. The authors hypothesized that the pathogenesis of fibromyomata may be related to an inherent abnormality in the myometrium (37). Stewart and Nowak proposed in 1998 that leiomyoma growth were initiated through a response to injury, which could cause transformation of the smooth muscle cells of the myometrium from a contractile phenotype to a proliferative-synthetic phenotype (38).

Potentiators and effectors

Uterine leiomyomas have significantly increased concentrations of both estrogen and progesterone receptors compared with normal myometrium (39,40). It has long been established that estrogen promotes leiomyoma growth. Recent biochemical and clinical studies have suggested that progesterone and progestin also enhance proliferative activity in leiomyomas (41). Both estrogen and progesterone and their receptors seem to play an important role in inducing leiomyoma growth, acting closely together. There are several possible mechanisms for sex steroids activity in leiomyomas. 17β-estradiol is found in higher concentrations in leiomyomas than in myometrium (42). It is speculated that reduced 17β-hydroxysteroid dehydrogenase, which normally metabolizes estrogen to estrone, may be a reason for this finding. The estrogen metabolite estradiol 4-hydroxylase is elevated in leiomyomas (43). This metabolite may function as a long-acting estrogen and possess potent estrogenicity. Progesterone up-regulates the estrogen receptors and also increases the

mitotic rate in myometrial tissue. These mechanisms may play a role, especially during the luteal phase when the progesterone level is high (8).

There are a number of growth factors with mitogenic activity that are identified in leiomyomas and may be some of the effectors of leiomyoma growth. Many of these factors may interact, sometimes resulting in a synergetic effect. In other situations, one growth factor is dependent on the presence of the other. The basic fibroblast growth factor (bFGF) that is stored in the extracellular matrix of leiomyomas, and the transforming growth factor β (TGFβ) may play an important role. The insulin-like growth factor (IGF) stimulates cell proliferation in uterine leiomyomas. Other growth factors like prolactin, the vascular endothelial growth factors (VEGF), platelet-derived growth factor (PDGF) and epidermal growth factor (EGF) are also thought to take part in the process of leiomyoma proliferation (8).

3.2 Risk of malignancy

Sarcoma of the uterus is an uncommon malignant tumor with a generally poor prognosis. Since the tumor is very difficult to distinguish from a benign leiomyoma both by clinical and radiological examinations, concerns have been expressed about leiomyoma treatment that do not involve tissue specimens for accurate pathological diagnosis.

The assumption that sarcomas do not arise from leiomyomas was supported by cytogenetic studies demonstrating that chromosome rearrangements in leiomyomas are distinct from the complex rearrangement and aneuploid karyotypes characteristic of leiomyosarcomas (44). However, a recent study has identified a subgroup of cellular leiomyoma with deletions of chromosome 1 that have transcriptional profiles that cluster with those of leiomyosarcoma (45). This finding has raised the theory that leiomyosarcomas may derive from certain rare histological and karyotypic variants of leiomyomas (46).

The incidence of sarcomas among patients with presumed uterine leiomyoma is found to be low, with estimates of 0.2-0.5% (3,47,48). The common assumption that rapidly growing leiomyomas should cause awareness of the diagnosis of leiomyosarcoma has never been verified. Parker et al. found an incidence of 0.27% of sarcomas in a study of 371 women operated on for “rapidly growing” leiomyomas. In the same study, the total incidence of sarcomas among 1332 patients that had surgery for leiomyomas was 0.23%. The authors reviewed the literature and found that only a total of 15 (2.6%) of 580 women with leiomyosarcomas had a history of rapid growth. The most common symptom was abnormal

bleeding, followed by pain and the presence of a pelvic mass (48). The average age of women with a diagnosis of sarcoma is 54-63 years (49). Thus, the diagnosis should be considered in a postmenopausal woman with a pelvic mass, abnormal bleeding, and pelvic pain (50).

3.3 Vascular anatomy of uterus and the ovaries relevant for uterine artery interventions

A detailed knowledge of the pelvic vascular anatomy is essential to perform both uterine artery embolization and laparoscopic occlusion of the uterine arteries safely. Because of the variability of the three-dimensional distribution of the internal iliac artery branches in the deep pelvis, the classic anatomic and radiological topography of the uterine artery might be difficult to understand for the surgeon. Angiographic and surgical experience reveals numerous anatomical variations of the location of this artery. Sometimes there are two instead of one artery, the artery may be replaced by small arterial branches or it may even be missing at one or both sides (51,52).

Most commonly the uterine artery arises from the internal iliac artery (hypogastric artery). It descends parallel to the pelvic wall until the level of the cervix where the artery transverses medial against the uterus and invariably crosses above the ureter. When the artery reaches the lateral uterine wall it divides into the ascending and descending (cervicovaginal) branch. The main stem of the artery ascends along the uterus at the medial edge of the broad ligament. For the interventional radiologist, the uterine artery is found as the first or second branch of the anterior division of the internal iliac artery (from the inferior gluteal artery) in 51% of the cases (51). The gynecologist may follow the ureter downwards to locate the uterine artery where it crosses above it. If uterus is large and the view restricted, it might be easier to follow the obliterated umbilical artery proximal to the origin of the uterine artery.

Less common the uterine artery arises from the internal pudendal artery. It is crucial to be aware of the other parietal branches of the internal iliac artery in this area. The superior vesical artery often origins from the umbilical artery distal to the uterine artery, but may also have other locations. Similarly, the medial rectal artery and the obturator artery arise variably from the internal iliac artery in the same area (52). The uterus has a rich blood supply, mainly from the uterine artery (53). In addition, there exists a vast network of collateral arterial communication from the vagina, the aorta, femoral artery branches, and other lesser-known arterial collaterals (54,55). Collateral vessels and anastomoses often

become hypertrophic in the presence of uterine or ovarian lesions to supplement the increased vascular demand (56).
In women with leiomyomas, two different angiographic studies have reported utero-ovarian anastomoses in 46% and 40% of the patients (57,58). Controversy exists about the direction of flow in these anastomoses. In an angiographic study of 76 patients, there was flow from the ovarian artery to the uterine artery in 22% of the cases, direct supply from the ovaries to the leiomyoma in 3.9% (57). Two other angiographic studies have revealed direct supply from the ovaries to the leiomyoma in 5% and 6% of the cases respectively (59,60). Intramural intrinsic uterine arteries consist of ascending and descending, arcuate, radial, and peripheral arteries leading to free flow through the uterus. Leiomyomas receive their primary blood supply from the end arterioles of the uterine artery (53). Bilateral occlusion of the uterine artery prevents collateral flow to the leiomyoma from the contralateral artery.

The blood supply to the ovaries varies also between individuals. The main ovarian artery generally originates from the aorta below the level of the renal arteries and has a characteristic tortuous course when examined at angiogram (59). According to Borell et al., who performed angiographic studies already in 1954, the ovary is supplied from the ovarian arteries only in 40% of cases, both by uterine and ovary arteries in 56% of cases and by uterine arteries alone in 4% of the cases (61). In a recent angiographic study of women with leiomyomas, Razavi et al. found that the major blood supply to the ovaries was from the uterine artery in 6% of the cases (57).

3.4 Diagnosis

The diagnosis is usually made by a standard gynecological examination including transvaginal and/or abdominal ultrasonography. In most cases, leiomyomas have a characteristic appearance on ultrasonography with a sharp demarcation against surrounding myometrium. Commonly they appear as well-defined, hypoechoic lesions that are rounded in contour. The tumor may also have a more complex, inhomogeneous appearance with cystic changes. Usually the diagnosis is easy. However, to tell the difference from a leiomyosarcoma is not possible based on ultrasonography. When the leiomyoma is calcified, it causes acoustic shadowing that sometimes makes the visualization difficult. Saline infusion sonography is useful to diagnose submucous leiomyomas and is essential as preoperative evaluation before hysteroscopic resection.

Magnetic resonance imaging (MRI)

MRI examination is increasingly being used in diagnostic of leiomyoma disease. The advantage of MRI is that it does not involve any ionizing radiation and that the images have superior contrast resolution. The disadvantage of MRI is that the examination is time and cost-consuming and the availability is limited. An MRI scanner consists of a large circular magnet housed in a gantry within which the patient lies. The system depends on the behavior of the hydrogen nucleus (proton) in tissues when it is exposed to radio-frequency signals inside a strong magnetic field. When the protons relax to its normal position, weak radio-signals are sent back to the receiver inside the magnetic scanner. A map of the distribution of the signal is built up in a computer that produces the images. The strength of the signals depends not only on proton density but on two relaxation times; T1 and T2 that represent different occurrences in the complex movement of the hydrogen proton. The T1 and T2 weighting of an image can be selected by appropriate altering of timing and sequence of the radio-frequency pulses. Because the images depend on the hydrogen proton density in the tissue i.e. equivalent to their water or lipid content, the MR imaging is especially useful in the evaluation of soft tissue.

A study performed to compare the accuracy of MRI and transvaginal ultrasonography in the diagnosis of leiomyomas in women scheduled for hysterectomy showed that the two diagnostic tools are equivalent in detecting the presence of leiomyomas. However, the study showed that MRI is superior in assessing the number of leiomyomas, in the diagnosis of adenomyosis and to measure the leiomyoma size accurate when more than 4 leiomyomas are present in one uterus (62). Another study compared MRI and a combination of abdominal and transvaginal ultrasonography in women with leiomyomas referred for uterine artery embolization. This study showed that MRI was superior to ultrasonography in the diagnosis of leiomyoma location, number of leiomyomas and volume of the uterus, however not in assessing the volume of the largest leiomyoma (63). The intra-observer reproducibility of uterus evaluation by MRI, transvaginal ultrasonography, saline infusion hysterosonography and hysteroscopy was compared in a study by Dueholm et al. This study showed that MRI was significantly less observer dependent than the other diagnostic techniques. Intra-observer agreement for MRI in exclusion of intracavitary abnormalities, detection of submucous leiomyomas and identification of leiomyomas was 0.97 for all three variables. For detection of intracavitary polyps, the intra-observer agreement for MRI was 0.49 (64). The inter-observer reproducibility of MRI assessment in women with leiomyomas

was confirmed by Volkers et al. The investigators found also good intra-observer reproducibility, except for the presence of adenomyosis where a kappa-value of 0.55 and 0.66 was found for each of two observers (65).
Adenomyosis might be difficult to diagnose both with ultrasonography and MRI. According to the two above mentioned studies, MRI was found to be superior to ultrasound with regard to intraobserver reproducibility in the presence of adenomyosis. Both studies found an inter-observer agreement of 0.73 for this finding on MRI. Diffuse adenomyosis is characterized as irregular, homogenous thickening of the endometrial-myometrial junctional zone both on ultrasonography and MRI. On MRI, this thickening has a low signal-intensity. Adenomyosis foci in the myometrium can be seen during ultrasonographic examination as heterogeneous, hypo-eccogenic areas with or without cysts. On MRI-examination, the foci are manifested as high signal intensity lesion with ill-defined margins. Byun et al. found that T2-weighted images were superior to T1 contrast-enhanced images in the evaluation of both the junctional zone thickening and the adenomyosis foci within the myometrium (66,67).

Paramagnetic agents may be used during MRI examinations to produce contrast by decreasing T1 relaxation time in specific locations of the body. Intravenous administration of gadopentetate dimeglumine (gadolinium) is commonly used for this purpose. With the use of gadolinium-enhanced MRI, it is possible to evaluate the degree of degeneration or viability of the leiomyomas (68).
Leiomyoma and uterus volume may be calculated from MR images either by the use of three perpendicular diameters incorporated in the equation of an ellipsoid (69,70) or by serial measurements of regions of interests (ROIs) on scan sequences (71).

MRI measurement is a useful tool in modern research aimed at evaluating new conservative treatment modalities for leiomyomas. In countries like Norway, where ultrasonography is an integrated part of the examination performed by gynecologists, MRI examination for patients with leiomyomas are only occasionally indicated in daily practice. MRI examination is useful when the ultrasonographic diagnosis is uncertain, for preoperative mapping of multiple leiomyoma location before myomectomy in selected cases or in patients that are unable to go through a gynecological examination.

3.5 Indication for treatment

The most common indication for treatment of leiomyomas is menorrhagia, often accompanied with dysmenorrhoe and bulk symptoms. The patient's own interpretation of the severity of symptoms is often the most important indication for treatment in modern practice. Anemia might occur, however most patients referred for treatment of leiomyoma symptoms including menorrhagia have hemoglobin levels within normal range (72). Urinary frequency is a common complaint with large uteri. Discomfort because of pressure are more common than distinct pain (73). Hydronephrosis or bowel constipation because of pressure from huge leiomyomas is rarely seen, however such occurrences are reported in the literature (74). Infertility or subfertility is in some cases indication for treatment of leiomyomas. However, this issue is controversial and considered outside the limits of this thesis.

Many women do not want to remove their uterus even though they have considerable complains of menorrhagia and or bulk symptoms. The reason for this is complex. Some women want to preserve their fertility. Other feel that the uterus is important to their feeling of femininity; they might be afraid of dysfunction of their sexual life, or they simply fear the anesthesia or the surgical procedure itself (75).

3.6 Treatment options

The following sections provide an overview of the current uterine-sparing treatments available or under investigation, including the three modalities studied in this thesis; Laparoscopic uterine artery occlusion, uterine artery embolization, and the transvaginal, Doppler-directed temporary clamp.

3.6.1 Medical treatment

In order to maintain organ preservation and avoid surgery, a lot of different medical treatment modalities for symptomatic leiomyomas are proposed.

Nonsteroidal anti-inflammatories, oral contraceptive pills, and progestins are aimed at minimizing abnormal menstrual bleeding or controlling pelvic pain. These treatments are associated with minimal cost and risk, but their effectiveness in women with leiomyomas has not been systematically studied. The levonorgestrel intra-uterine device (LNG-IUS), is effective in reducing menstrual bleeding in women with menorrhagia with and without leiomyomas and should be considered as an alternative to hysterectomy in such women

(76,77). However, the use of LNG-IUS in women with leiomyomas is not investigated in any RCTs. The risk of spontaneous expulsion of the intra-uterine device in women with large leiomyomas is commonly considered as a relative contraindication to the use of the LNG-IUS. This occurrence is reported at various intervals in some women. However, in one study, the women wanted re-insertion of the device because of the remarkable effect on the menorrhagia (78). MRI measurements of leiomyoma and uterus volume before insertion and after 12 months have not shown any significant volume reduction during the use of the LNG-IUS (77,78).

There are numerous agents investigated for the conservative treatment of leiomyomas:

Gonadotrophin-releasing hormone analogs (GnRHa)
Gonadotrophin-releasing hormone analogs with agonistic or antagonistic properties have been shown to reduce leiomyoma size and menorrhagia significantly (79). Although undoubtedly effective on leiomyoma size and symptoms, there are considerably side-effects that includes menopausal symptoms and bone loss (80,81). These side-effects can be alleviated by the use of add-back therapy with estrogens, combined estrogens and progestins, tibolone or raloxifene without interfering with the efficacy of GnRHa (81-85). Unfortunately, recurrence of leiomyoma growth and symptoms occurs rapidly after discontinuing the GnRHa therapy (86). This fact, together with the expensiveness of the drug does not make it cost-effective for common use.
GnRHa has been used as pretreatment for myomectomy and hysterectomy, however, there are controversies related to the use of GnRHa on this indication. Increased risk of recurrence are reported, presumably because smaller leiomyomas shrink and are ignored at the time of surgery, only to regrow when the effect of GnRHa wear off (87). A Cochrane database systematic review concludes that the use of GnRHa for 3-4 months prior to leiomyoma surgery are beneficial for correction of preoperative iron deficiency anemia, reduce intraoperative blood-loss, operating-time, duration of hospital stay and rate of vertical incision. For patients undergoing hysterectomy, a vaginal procedure is more likely following the use of these agents. Evidence of increased risk of leiomyoma recurrence was equivocal (88). Dubuisson et al. found that treatment with GnRHa before laparoscopic myomectomy was one of the risk factors for conversion to laparotomy (89). Some claim that the GnRHa render surgical planes less distinct, making the enucleation of the leiomyoma more difficult (90) and the operating time is found significantly longer during laparoscopic

myomectomy in patients pretreated with GnRHa compared to those without (91). However, in an RCT subsequent to the Cochrane review, the authors did not find any differences in blood-loss during surgery, duration of surgery, operating time or hospital stay between women with and without pretreatment with GnRh-analogs. Furthermore, it was not possible to demonstrate any difference in cleavage planes among treated and untreated leiomyomas (92). A review of the cost-effectiveness of GnRh found that the costs outweigh its benefits (93).

Androgenic steroids (Danocrine and Gestrinone)
Until GnRha became widely used in treatment of endometriosis, the androgenic steroid Danocrine (Danazol) was the most common medical treatment for this condition.
Four months of Danazol treatment have reduced leiomyoma related symptoms and leiomyoma and uterus volume with up to 37% and 30% respectively, measured by ultrasonography (94). Danazol has been investigated as adjuvant therapy in continuum of GnRha therapy because of less menopausal symptoms and no bone loss observed (95). Side effects including weight gain, acne and edema are reported after treatment with Danozol for endometriosis, however lower doses are used for leiomyoma treatment and consequently less side effects are seen (94).
Another androgenic steroid, Gestrinone, is shown to reduce leiomyoma volumes and cause amenorrhoea, and effect of the treatment lasted up to 18 months after discontinuation of the therapy (96).

Selective estrogen receptor modulators (SERMs)
Raloxifen has been found to reduce leiomyoma size in postmenopausal women and in premenopausal women older than 40 years, however not in younger women (97). Potential serious side effects like thromboembolism are not fully investigated. Evidence is lacking regarding the usefulness and safety of this drug in leiomyoma treatment, and SERMs are currently not recommended for treatment of leiomyomas (98).

Antiprogestin (Mifepristone; RU-486)
This drug is well known for the gynecologist, as it is used for pregnancy termination in doses of 200-800 mg with or without misoprostol. Studies including a small randomized controlled trial (42 patients) have shown reduction of leiomyoma and uterus volumes of 40-50%, amenorrhoe in 40-70% of the patients, reduced anemia and leiomyoma related

symptoms and increased quality of life with doses of 5 or 10 mg. Simple endometrial hyperplasia was seen in 28% of the patients, less with the lowest dose. Adverse effects included vasomotor symptoms, however no change in bone mineral density during 12 months follow-up (99,100). A combination of RU 486 and LNG-IUS to prevent endometrial hyperplasia is proposed as a future alternative treatment (101). However, the safety with regard to the endometrium is necessary to clarify before larger studies are performed.

Selective Progesterone Receptor Modulators (SPRMS)

Asoprisnil (J867) and CDB-2914

This is a selective progesterone modulator with mixed agonist/antagonist activity that seems promising in leiomyoma treatment. This drug has inhibitory effect on the endometrium without substantial effect on the estrogen concentration. In addition, it inhibits proliferation and induce aptosis in leiomyoma cells (102,103).

In a recent randomized controlled trial (phase II-study), 129 patients were treated for 3 months with 5, 10 and 25 mg daily. Bleeding was reduced in 28, 64 and 83% of the women, respectively. On 25 mg dose, leiomyoma volume was reduced by 36% after 12 weeks measured by sonography. There were few side effects compared with placebo (104). Though the data are encouraging, the finding warrants replication through larger studies over an extended period of time.

Another SPRM (CDB-2914) is recently evaluated in a phase I study (105).

Aromatase inhibitors (anastrozole)

The evidence of the use of aromatase inhibitors to treat leiomyomas are limited to case-reports of peri- or postmenopausal women (106). The agents are unlikely to be effective in premenopausal women. The potential use of the aromatase inhibitor is suggested as an alternative to progestin in postmenopausal obese women with symptoms caused by leiomyomas (101).

Gabergoline

Gabergoline is a dopamine agonist with inhibitory effect on the secretion of GnRh. It is commonly used to inhibit lactation and in treatment of prolactinoma. Recently garbergoline was compared with GnRha in a randomized study. The authors found significantly reduced leiomyoma volumes in both groups, and gabergoline had fewer adverse effects compared

with GnRHa (107). Clearly, further studies are warranted to determine the usefulness of this agent.

All these substances are interesting approaches to the treatment of leiomyomas; however none of them are proven safe and efficient for long time use.

3.6.2 Surgical treatment

Hysterectomy

Abdominal hysterectomy is the most frequently performed surgery for treatment of symptomatic leiomyomas. In 2000, 4764 hysterectomies were performed in Norway, about 4438 due to benign disorders (108). The most common indication is leiomyomas, accounting for about 40% of all hysterectomies (109). Hysterectomy provides a permanent solution to menorrhagia and pressure symptoms related to an enlarged uterus. Complete relief of symptoms is found among 89% of the patients; however only 70% said that they would recommend the treatment to others (110). Clearly, this is a major surgical procedure with considerable morbidity. Recent studies have found complication rates for hysterectomy performed due to leiomyomas of 26% (110) and severe postoperative complications in 3.6% (111). The most common complication during hysterectomy is hemorrhage. A study of 446 women having hysterectomy indicated by symptomatic leiomyomas reported higher risk of complications as uterine weight increased. The need for blood transfusions were increased when the uterus weighted more than 500g compared with uterine weight less than 500g (112). However, mortality rate for hysterectomy is low and was found to be 0.6/1000 in a retrospective study published in 1985 (113). More recent, the mortality of hysterectomy in women under 50 years of age with benign indications is reported to be about 0.3/1000 (114). Hysterectomy might be made less invasive with laparoscopic or vaginal approach. However, with large leiomyomas the transabdominal approach with a vertical incision is the only available option today.

Myomectomy

The most frequently performed uterus preserving surgery for leiomyomas is the conventional abdominal myomectomy. Myomectomy has been stated to relieve leiomyoma related symptoms in 80% of women (3). However, there is little documentation to support this statement in the literature. A prospective, non-randomized study comparing

myomectomy and UAE reported that 75% of the women in the myomectomy group had a significant decrease in symptom scores after 6 months (115). As hysterectomy, myomectomy is a major surgical procedure. It is widely accepted that the procedure carries the risk of excessive blood loss and conversion to hysterectomy. However, newer studies do not support these concerns (116). Even with very large leiomyomas in a study of 91 women, there were no conversions to hysterectomy (117). Still, in the latter study, the mean blood loss was 800 ml, and the highest reported blood loss was 3000 ml. In the same study, complications included one bowel perforation, one bladder injury and one reoperation for incarcerated bowel. Nevertheless, case-control studies suggest that there may be less risk of intraoperative injury with myomectomy when compared with hysterectomy (116,118).

A major disadvantage of myomectomy is adhesion formation. This might compromise the fertility, cause pain, increase the risk of ectopic pregnancy and cause intestinal obstruction. In some studies with second look after abdominal myomectomy, adhesions were found in all patients examined (119-121).

In studies using life-table analyzes, the average 5-year clinical recurrence-rate is found to be approximately 10%. It is estimated that about 50% of the patients with recurrence needed secondary surgery with one out of three requiring hysterectomy. In these studies, the risk of recurrence was increases with multiple leiomyomas, and decreased with subsequent pregnancies (122).

Laparoscopic myomectomy is associated with reduced blood-loss, less febrile morbidity and shorter recovery time after the procedure (123). In addition, second look studies after abdominal and laparoscopic myomectomy have shown less postoperative adhesions (124). The wide application of this approach is limited because of the technical difficulty of the procedure especially with regard to the suturing of the myometrium. The cumulative 5-year recurrence rate after laparoscopic myomectomy was reported to be 51.5% in one study (125). Another study published a follow-up of 192 women, and found 17% recurrence after 5 years (126). The authors concluded that the recurrence rate may be higher after laparoscopic than after abdominal myomectomy, but considered the low morbidity to be a major advantage of the laparoscopic approach.

Adhesions may be prevented by the use of adhesion barriers both during abdominal and laparoscopic myomectomy. There are a number of such agents available that all seems to reduce adhesion formation significantly (127-130).

Concerns have been expressed about the risk of uterine ruptures during pregnancy and delivery after myomectomy. The general risk of uterine rupture is found to be 0.35/1000,

with a risk of 6% after cesarean section and a risk of 0.02% for those who had no previous cesarean (131). Spontaneous uterus ruptures have been reported, both after abdominal and laparoscopic myomectomy, however the incidence seems to be no higher than 1% and is probably dependent of a proper repair of the myometrial incision and carefulness with the use of electosurgery (132-135).

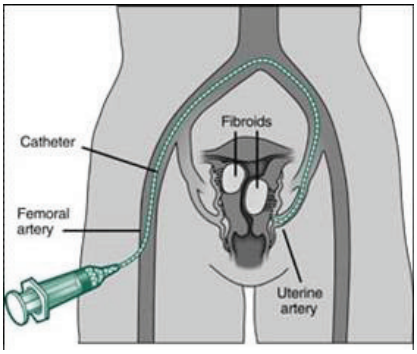
There is no scientific evidence in the literature to support increased fertility after myomectomy for intramural or subserous leiomyomas. However, numerous observational studies reports pregnancy- and delivery rates ranging from 10-75% after both abdominal and laparoscopic myomectomy (87,136-140). Currently, myomectomy is the treatment of choice for women with symptomatic leiomyomas who desires fertility.

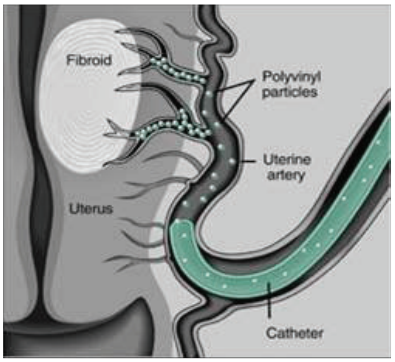
Transcervical Resection of Myomas (TCRM)

Submucous leiomyomas may be removed hysteroscopically. If more than 50% of the leiomyoma is protruding into the uterine cavity and the diameter is less than 3-4 cm, it is considered possible to remove by a resectoscope (TCRM) (141). This procedure has low complication rate and short recovery time (142). However, a relatively high number of procedures are needed to reach the level of skills that is mandatory to perform the procedure safely. Approximately 10% of the patients need repeated surgery within 5 years (143,144). No studies have confirmed the association between submucous leiomyomas and menorrhagia, however, most trials show a reduction in bleeding after resection (143-145). Studies support an increased pregnancy rate after hysteroscopic resection of submucous leiomyomas compared to controls (146,147).

3.7.3 Uterine Artery Embolization (UAE)

Transcatheter arterial embolization for treatment of postpartum hemorrhage was introduced 30 years ago (148). The effect of uterine artery embolization on uterine leiomyomas was first described by Ravina in 1995 (149). UAE is performed by placing a catheter into the femoral artery and accessing both uterine arteries under angiographic guidance. To insert the catheter, a skin incision is made on one or both sides in local anesthesia. Embolic agents are then injected into the uterine arteries. Because the leiomyomas are mainly supplied by this artery, the procedure usually interrupts their blood supply. Most commonly polyvinyl alcohol (PVA) particles or Tris-acryl Gelatin Microsphers (TAGM) are used as the embolic agent.





The procedure involves considerably post procedural pain and a substantial amount of narcotic painkillers are often needed the first 24 hours after treatment. The pain is thought to be due to global myometrial ischemia until normal myometrium establishes a new blood supply through collateral vessels from the adjacent organs (150).

Postembolization syndrome occurs in approximately 40% of the patients (151,152). It is defined by low-grade fever, pelvic pain, nausea, vomiting, loss of appetite and malaise in the first week after treatment. This symptom complex is regarded as an expected aspect of recovery due to the necrotic process. The degree of intensity of these symptoms is variable and the occurrence is only regarded as a complication if unplanned medical therapy or hospitalization is needed (153).

Radiation exposure to the ovaries during the procedure is estimated to approximately 22 cGy (154). Exposure may be considerately alleviated by reducing the field size, pulsed fluoroscopy, limited DSA imaging and bilateral femoral puncture.

More than 50 000 procedures have been performed worldwide (http://www.fibroids.com) about 30 000 of them in the US (114). Prospective single center studies have reported relief of excessive menstrual bleeding in 81-96% of the patients and reduction in bulk symptoms in 61-92% of the patients 3-24 months after treatment (151,152,155-161). Reduction in uterus volume of 23-53% and reduction of the dominant leiomyoma volume of 37-68% measured by ultrasonography or MRI are found 3-12 months after treatment (151,152,156-159,161-164).

In 1999, The Society of Interventional Radiology Foundation established the Fibroid Registry for Outcomes Data (FIBROID). This registry includes 3000 patients from 17 treatment centers. According to the FIBROID, 82% of 1701 patients claimed satisfactory outcome when answering questionnaire 12 months after treatment with UAE. At the same

point in time, there were no improvement of symptoms in 5.5% of the patients, and 2.9% required hysterectomy (160). Long-term results are not published from the FIBROID, however, single-center studies have reported 5-year recurrence rates of 11- 20% (165-167). Although major complications might occur during or as a result of UAE, they are rare. The table shows the reported complication rates after uterine artery embolization published by the joint Standard of Practice Committee of the Cardiovascular and Interventional Radiology Society of Europe (CIRSE) and the Society of Interventional Radiology (SIR) in 2004 (153).

Complication rate for UAE	**(%)**
Transient amenorrhea	5-10
Permanent amenorrhea < 45 years	0 -3
> 45 years	7-14
Leiomyoma expulsion	0 - 3
Non-infectious endometritis (chronic discharge)	1 - 2
Endometrial or uterine infection	1 - 2
DVT or pulmonary embolus	< 1
Uterine necrosis	< 1
Non-target embolization	< 1

Total uterine necrosis with risk of infection and sepsis may indicate acute hysterectomy. This occurrence is reported in 1/305 and in 3/400 in two of the early studies (151,159). The short-term outcome data from the FIBROID reported 3 (0.1%) hysterectomies during the first 30 days after admission from hospital, although the indications were not specified (168).

Two cases of fatal sepsis have been published after UAE (169,170). Three other deaths has been reported following UAE; a case of postprocedural pulmonal embolism and two of unknown causes (171,172).

The risk of ovarian failure after UAE is believed to be caused by unintended embolization of a hypertrophic utero-ovarian vessel not discovered during the embolization procedure or by embolization of a uterine artery that provides the only blood supply to the ovary (51). In one recent study, where anti-Müllarian hormone measurements were used as indicator of premature ovarian failure, ovarian function after UAE was found to be decreased to the same level as after hysterectomy (173).
Transcervical leiomyoma expulsion is defined as detachment of leiomyoma tissue from the uterine wall and subsequently transvaginal passage. This process is often associated with vaginal bleeding, discharge, abdominal pain and/or fever. Surgical intervention may be necessary either with D&C, hysteroscopic resection or occasionally hysterectomy. Some authors propose a higher risk of this occurrence with submucous located leiomyomas. However, this is questioned by others (153,174).
Gynecologists have expressed concerns about adhesion formation after UAE. In a case-control study of 30 hysterectomies after UAE, there were significantly more patients (20%) with adhesions in the group with previous UAE compared to 1.4% among the controls (175).

The absolute contraindications to UAE are ongoing pregnancy or infections. Suspicion of malignancy in the uterus or ovaries would be a contraindication, unless the procedure aims to palliate such a condition.
Relative contraindications to any endovascular intervention include coagulopathy, contrast material allergy and renal impairment. Relative contraindication to uterine artery embolization would be conditions that reduces the normal healing process; immunocompromise, chronic endometritis, previous pelvic radiation or surgery (153). Desire to maintain childbearing potential is still a relative contraindication, since preservation of fertility cannot be assured according to the existing literature. However, there are several pregnancies reported after UAE. Walker et al. reported 56 pregnancies after 1200 embolization procedures, of which 33 (58.9%) had a successful outcome (176). A randomized study compared fertility outcome of 40 women after myomectomy and 26 after UAE who tried to conceive. There were significantly more pregnancies (83%), labors (48%) and fewer abortions (18%) after myomectomy than after embolization (65% pregnancies, 19% labors, 53% abortions). However, the study was obviously not randomized on the basis of desired pregnancy (177). For women who wish to maintain childbearing potential, UAE

may be performed as treatment for leiomyoma symptoms if hysterectomy is the only alternative option.

There are different types of embolic agents available. In the first published series, PVA particles were used. The outcome with the use of this agent was satisfactory on both short and long term (165,166). More recently tris-acryl gelatin microspheres (TAGM) have shown the same level of durable symptom control (178). Resorbable gelatin sponge particles have been used by Katsumori et al. in a trial with 96 patients. Eighty patients were followed up to 5 years with a recurrence rate of only 11% and reintervention rate for all reasons of 13% (167). The use of spherical PVA have been investigated in different protocols with less satisfactory results (179,180).

Factors associated with outcome of clinical symptom relief and leiomyoma reduction short time after UAE have been investigated by many authors. Pretreatment leiomyoma diameter of more than 8.5 cm measured by ultrasound were associated with more clinical failures in a study of 300 patients followed for 5 months (181). This finding could not be confirmed by MRI examination of 114 women and 2 years follow-up in another study (182). However, Spies et al. found, after adjustment for other variables; that larger baseline dominant leiomyoma volume on MRI measurements before treatment was associated with less bleeding reduction. In addition there were less reduction in leiomyoma volume after 3 and 12 months in the same group of patients (183).

Submucous location of the leiomyomas before treatment was found to result in significant larger uterus volume reduction measured by MRI 3 months after treatment compared to other locations in two studies (183,184). Any certain link to clinical result was not found (182,183,185,186).

The vascularization of the leiomyomas has been examined by gadolinium-enhanced MR images before treatment in several, however small, trials. All studies indicate that leiomyomas that are well perfused before UAE treatment respond better to UAE treatment than poorer perfused leiomyomas (184,185,187).

The T1 and T2 signal characteristics of the leiomyomas before treatment have by some authors been reported to be an important predictive sign of leiomyoma volume response to treatment. Two authors have claimed that a high signal intensity on T1-weighted images and a low signal-intensity on T2 weighted images before treatment corresponded with less reduction on leiomyoma volume after treatment (187,188), and one found only this association for the T1-weighted image (184). Watson and Walker found that high signal intensity on T1-weighted images was uncommon and did not appear to alter the outcome.

They found, however, among 114 women examined, that high pretreatment signal intensity on T2 weighted sequences was associated with a good response on volume reduction and patient outcome. A low signal intensity was associated with less shrinkage, but good outcome for the patients symptoms (182).

Several investigators have claimed that complete leiomyoma infarction after treatment is essential to avoid regrowth of leiomyomas and recurrence of symptoms both on short-term (189) and long-term recurrences (190,191). It is reasonable to assume that this statement is correct, however the number of cases studied is limited, and adjustment for other variables is not performed. Thus there is not yet any scientific evidence to confirm this assumption.

There is limited evidence of predictive factors on long term result. Spies et al. reported clinical outcome of 3-60 months follow-up in 200 patients. The authors found higher risk of failures with baseline leiomyoma volume larger than the median, among those not improved at 1 year and three times higher risk of failure for women with less than or equal to median percent reduction of leiomyoma volume at 3 months after UAE (165).

Gabriel-Cox et al. studied data from 562 women from 8 different treatment centers with a follow-up of median 4.8 years after UAE. They found that only unilateral uterine artery embolization predicted subsequent hysterectomy with a relative risk of 2.19. Age, indication, uterine-volume, embolic agent or radiologist experience did not influence on the hysterectomy rate (192).

Comparison with myomectomy and hysterectomy

Comparison with myomectomy have shown shorter hospital stay and recovery time (115,193,194) and less in-hospital complications after UAE (115,193,195). Symptom reduction is reported with larger variations; UAE was better in one study (196), similar in another (115), better with regard to menorrhagia and poorer for bulk symptoms in a third (194).

Three randomized controlled trials have compared UAE with hysterectomy. Shorter hospital stay and less time to full recovery after UAE were found in all studies (197-199).

Complication rate is more variably reported. Two of the studies concluded with less complications after hysterectomy, and one found less major complications after UAE compared to hysterectomy (199). The latter finding was supported by a large retrospective multicenter (HOPEFUL) study (200). The HOPEFUL study found that the hysterectomy group reported more complete relief of their leiomyoma-related symptoms; however that only 70% of the participants in this group would recommend the procedure to a friend

compared to 86% who would do that after having experienced UAE. Cost-effectiveness analyses over a period from 1 to 5 years after treatment favors UAE in studies from Europe, USA and Canada (199,201-204). In a Chinese setting, You and co-writers found hysterectomy more cost-effective over a 5-year period compared to hysterectomy and myomectomy (205).

3.6.4 Myolysis

A number of focused energy delivery systems based on radiofrequency, bipolar electricity, Yag-laser, microwaves and cryogenic probes have been investigated to destruct leiomyoma tissue (206-208). Delivery of the energy is applied transvaginal or during laparoscopic or hysteroscopic guidance. Clinical evaluation has mainly been confined to case series with apparent effect on leiomyoma size and reduction of bleeding symptoms (209,210). Although uneventful deliveries are reported after myolysis treatment (211), most investigators do not recommend this treatment for women who desire pregnancy because of potential risk of uterus rupture, abnormal placenta development and adhesions (212). Longer term comparative trials are required to evaluate and compare myolysis with other leiomyoma treatments.

MR-guided high intensity focused ultrasound (MRgFUS) is performed by interventional radiologists (213). A focused high-frequency, high-energy ultrasound beam is used to thermally destruct leiomyoma tissue. The extent of treatment is supervised by a MRI-based volume and thermal real-time measurement system. Although the treatment is performed without incisions and with a very fast recovery for the patients, there are considerable limitations of the use. Only small parts of the leiomyoma have been treated at a time in the published studies, and the need for additional therapy appears to be high (214). MRgFUS cannot be used on leiomyomas located near sensitive organs like bladder or the bowel. In addition, the procedure is time-consuming and the equipment needed to perform the procedure is expensive. However, if the technique continues to develop and further studies are performed, the modality may find a place in the field of non-invasive leiomyoma treatment.

3.6.5 Laparoscopic bilateral occlusion of uterine arteries (LUAO)

In a Nordic paper published in 1895, Kuhn refers to the first reported procedure of surgical uterine artery occlusion as treatment for leiomyomas and menorrhagia. This procedure was performed by Rydygier and published in Wiener Wochenschrift in 1889.
Kuhn himself reports 34 cases performed by 8 different surgeons in Denmark and Norway (215). Follow-up was 1-12 months. Nineteen patients had good effects on bleeding reduction and leiomyoma size. For nine patients the follow-up result was stated as "a positive impression". One had no effect. One had recurrence of symptoms after 3 months; another had recurrence after 12 months. Three women had some, but not complete effect of the treatment. The technique used was ligation of the left and right artery by vaginal approach in 32 cases, and by open abdominal approach with additional closure of the round ligament and the ovarian ligament in 2 cases.
Since this initial report, the use of this treatment modality has been only occasionally reported until the first description of the modern variant of this treatment modality in 2000 (216,217). By laparoscopic approach and bipolar coagulation, Liu et al. occluded the uterine arteries and the anastomotic sites of the ovarian arteries. The authors published the year after a 7-12 months follow-up on the first 87 patients and reported that 93% of the patients had reduced menstrual bleeding. Ultrasonographic measurement of uterus and leiomyoma volume reduction was 46% and 76% respectively (218). Smaller studies, with a follow-up of 3-36 months have reported similar results, however the leiomyoma volume reduction in the studies by Holub and Simsek was 48 and 49% 12 months after treatment measured by ultrasonography and MRI (219-221). Simsek et al. used the pictorial blood loss assessment chart (PBAC) and found significantly reduced score (43%) among 21 patients 12 months after treatment. All authors have reported very moderate pain after the treatment.
Complications have been reported to be minor, however only one paper describes the complications after laparoscopic occlusion systematically (222). Holub et al. investigated 114 patients treated at 2 endoscopic centers in the Czech Republic retrospectively. No intraoperative complications were registered. A total of eight patients (7%) experienced postoperative complications within 30 days after surgery, with one of the women experiencing two complications, resulting in nine complications. In 5 patients, six early postoperative complications occurred: One port site bleeding, 4 patients with fever was successfully treated with antibiotics and one woman had sign of obturator nerve affection that was resolved with anti-inflammatory drugs and electostimulative convalescence

therapy. In addition, two patients were reported to experience leiomyoma necrosis that was treated with hysterectomy in one and myomectomy in the other. In addition, one patient was diagnosed with an endometrial stromal sarcoma one year after the laparoscopic treatment (222).

Recurrence of symptoms occurred in 10 (9%) of 114 patients 24 months after treatment in one study and in 27 (28%) of 95 patients after 48 months in another study (222,223).

Pregnancies after treatment with LUAO have been reported (223-225). One author have expressed concerns about a relatively high rate of early miscarriages, however, no cases for control were provided in that study (224). In another study, pregnancy outcome in 34 patients after UAE and laparoscopic occlusion of the uterine arteries were compared. In this study, higher rates of early miscarriages were found after UAE compared to after laparoscopic uterine artery occlusion (226). However, the appropriateness of both these treatment modality for women who desire fertility is still unclear.

Studies that compare outcome of symptom relief, volume reduction of uterus and leiomyomas or recurrence rates with other uterine sparing treatments are not published, with exception for the papers presented in this thesis.

3.6.6 Temporary Doppler-directed transvaginal uterine artery occlusion (D-UAO)

Transvaginal occlusion of the uterine arteries can be performed by placing a specially designed clamp in the vaginal fornices and, guided by Doppler ultrasound auditory signals, positioning it to occlude the uterine arteries (227). Such a clamp has been developed to temporarily occlude the uterine arteries in order to treat uterine leiomyomas. The clamp is left in place for 6 hours and then removed.

Similar to UAE and LUAO, this treatment is based on the principle of depriving leiomyomas of blood supply to cause tissue death. The rational basis for a temporarily occlusion to treat leiomyomas is based on the theory of transient uterine ischemia (150). According to this theory, only a certain period of time of ischemia is necessary to cause the death of leiomyomas because they are more vulnerable to ischemia than the surrounding normal myometrium. Perfusion studies by MRI and computer tomography performed after uterine artery embolization indicates that blood initially clots in the vessels of both myometrium and leiomyomas. After a period of time, the blood clots disappear inside the vessels of healthy myometrium, but not inside the vessels in the leiomyomas (150). The myometrium survives until blood flow is re-established, but during the time the

myometrium is ischemic the leiomyomas die due to its insufficient blood supply. It is hypothesized that the leiomyoma tissue are less able to lyse clots that form inside the vessels after ischemia and also less able to recruit collateral flow. Findings of a greater amount and higher activity of fibrinolytic enzymes in normal myometrium compared to leiomyomas support this theory (228). The greater micro vascular density in the myometrium compared to the leiomyomas may contribute to this, since the fibrinolytic enzymes are concentrated in the endothelium of the vessels (22,229).

If the uterus survives severe ischemia and the leiomyomas do not, the next question will be; how long time of ischemia is necessary to cause leiomyoma death?

Reports of CT scans with the use of contrast medium performed 6 and 24 hours after uterine artery embolization showed wash-out of medium from myometrial tissue, indicating that by this time the reperfusion of the myometrium had already started. The same scans showed contrast medium still trapped inside the leiomyomas, and no wash-out (230). In another study, contrast-enhanced MRI was performed within 30 minutes after UAE. Immediately following embolization, there was a dramatic reduction in the overall uterine perfusion, however, while perfusion of the myometrium reduced from a maximum enhancement (ME_{90}) of 110 before embolization to a ME_{90} of 26% immediately following embolization, the perfusion of the leiomyomas had virtually stopped. After 1 and 4 months, perfusion in the myometrum recovered to normal levels, while leiomyoma perfusion remained extremely poor (231). The investigators state that the immediate difference in perfusion response between myometrium and leiomyomas is most likely a result of collateral circulation and the size of the vessels supplying the myometrium since the myometrial vessels tend to be larger (22,232).

The rationale for the six-hour duration of the occlusion with the vaginal clamp is derived from a study of laparoscopic bilateral uterine artery permanent occlusion with pH-measurements of the myometrium in continuation of the procedure. The pH-values measured indicated that the myometrium was reperfused within six hours after occlusion of the uterine arteries in about 80% of the patients (233).

A subsequent study in 10 women with laparascopic treatment of leiomyomas documented that the clamp was kept in place for a time period of between 10 to 59 minutes in all of the ten patients (234).

4. AIMS OF THE STUDY

This study aims to explore uterine-sparing treatments for women with symptomatic uterine leiomyomas. We wanted to investigate alternative modalities to occlude the uterine arterial supply.

More specific, we aimed to

1. Investigate the short and long term effect of bilateral laparoscopic occlusion of uterine arteries compared to uterine artery embolization.

2. Compare the 6-month MRI results of laparoscopic occlusion of uterine arteries with uterine artery embolization and investigate how the results related to the clinical outcome.

3. Determine whether it was feasible to occlude the uterine arteries temporarily by a Doppler-directed vaginal clamp.

5. MATERIALS AND METHODS

5.1 Approvals

The studies had approval from the Regional Committee for Medical Research Ethics in Eastern Norway and from Ullevål University Hospital's Advisory Committee on the Protection of Patient Records. The study protocol for the randomized study presented in paper II and V were published at the www.clinicaltrials.gov website (NCT00277680).

5.2 Patient selection and pre-treatment evaluation

The patients were recruited among premenopausal women with symptoms of uterine leiomyomas referred to the university clinic, who expressed a desire to avoid hysterectomy. Inclusion criteria were the women's own interpretation of increased amounts of menstrual bleeding (menorrhagia) and/or pressure symptoms. The preoperative examinations included a gynecological examination, ultrasonography, cervical smear and endometrial biopsy. Exclusion criteria included suspicion of malignancy, active pelvic inflammatory disease, known adenomyosis, menopause as well as pregnancy or desire for future pregnancy stated by patient. Additional exclusion criteria were uterus size exceeding the umbilical level and subserous leiomyomas that could easily be removed by laparoscopic surgery. Submucous leiomyomas with a diameter of less than 3.5 cm with an intramural extension of more than 50% were considered more suitable for hysteroscopic resection and were therefore excluded. Patients on hormones, specifically estrogens, progesterone, gonadotropin-releasing hormones or birth control pills within the last two months were also excluded.

Specific inclusion criteria for the study presented in paper III and IV were age above 18 years and no use of IUD, any intravaginal pessaries or other devices. The gynecologist had to be able to locate the position of both uterine arteries during Doppler ultrasound examination.

Specific exclusion criteria for the studies presented in paper I, II and V were contraindications against surgery and age less than 30 years.

Written informed consent was obtained from all the participants when it had been established that they met all eligibility criteria.

5.3 Randomization

(Paper II and V)
Randomization of 1:1 was undertaken in a total of seven blocks of 10 patients, using sealed envelopes. Five envelopes in each block of ten were assigned to laparoscopic treatment and five to uterine leiomyoma embolization. The envelopes in each block were closed, mixed and then numbered. Treatment was decided by drawing the next available envelope in ascending numerical order.

5.4 Outcome measures

Pictorial blood loss assessment chart (PBAC)
This was the primary outcome variable in paper I and II, and one of the secondary outcome variables in paper III and IV.

PBAC is a self administered pictorial chart, which, in addition to record the number of sanitary pads and tampons used, also takes into account the degree to which individual items are soiled with blood, passage of blood clots and episodes of flooding. After the inclusion into the studies, the women were given the chart together with oral and written instruction for use. The chart was filled in by the participants during the last menstrual period prior to treatment, as well as in advance of each outpatient appointment up to six months after the initial treatment. The participants were encouraged to use the same type of sanitary pads and/or tampons during the study period. The percentage change in pictorial blood loss assessment chart score for each individual was calculated and compared in order to minimize possible bias generated by women using different types of sanitary pads and tampons.

BLOOD LOSS SCORE

Towel \ Day	1	2	3	4	5	6	7	8	Score
 Score 1									
 Score 5									
 Score 20									
								Total towel score	

									Total
CLOTS S=1, L=5									
FLOODING									

Tampons \ Day	1	2	3	4	5	6	7	8	Score
 Score 1									
 Score 5									
 Score 10									
								Total tampon score	

									Total
CLOTS S=1, L=5									
FLOODING									

Pictorial Blood loss Assessment Chart (English version for illustration)

Patient assessment of symptoms

Paper I, II and V: Symptoms of menorrhagia and pressure were recorded using a simple standardized questionnaire by outpatient visits. The participants were asked to grade their bleeding amount as "little", "moderate", "heavy" or "very heavy". Bulk symptoms including urinary frequency were recorded "yes" or "no". The patients were also asked to grade changes in bleeding and bulk symptoms as "better", "worse" or "unchanged" compared to pre-treatment condition.

Paper V: The original consent included a 6-month follow up. Patients with no primary failure signed consent for extended follow up at this point. We surveyed the study participants about their present leiomyoma related symptoms by outpatient visits, telephone or letter to the patients at 12 months and thereafter annually until hysterectomy or menopause. The same questionnaire as described above was used, however this time with additional questions about menopause and subsequent leiomyoma related treatment. In cases of increasing bleeding, an endometrial biopsy was performed to exclude malignancy. Symptom recurrence was defined as new symptoms or worsening of symptoms that occurred more than 6 months after treatment, with or without repeated intervention.

Postoperative pain and nausea measured by a visual analogue scale (VAS):
(Paper I and II)
A visual analogue scale was used to evaluate the postoperative pain, nausea and headache. Every 4th hour the first 12 hours after treatment and then every 6th hour the next 24 hours, the patients were asked to set a mark on a 10 cm long line depending on their own perception on the severity of symptoms. They were told that the beginning of the line represented no symptoms and that the end represented the worst imaginable symptoms. There was no scale or mark on the lines. After the patients were admitted from hospital, one of the investigators (KH) measured the length in cm from the beginning of the line to the patient's mark. The average length, number of marks, the maximum symptom score and the time for the maximum symptom score were registered.

Postoperative painkilling regime (Paper I and II): All patients received a fixed regime of postoperative painkillers that contended of a nonsteroidal anti-inflammatory drug (diclofenac suppositories 50 mg three times/24 hours) and a paracetamol-codeine phosphate

combination (paracetamol 800 mg + codeine 40 mg four times/24 hours). The ketobemidon was given in variable doses by a patient-controlled intravenous pump.

Duration of hospital stay (Paper II): All patients were told that the expected stay in the hospital was 2 days. The actual stay was recorded for all participants.

Recovering time (Paper II): All patients were given 14 days of sick-leave or (if they did not have any paid employment) they were told that they needed 14 days to full recovery. The actual time to recovery or return to work was recorded at the one-month- or three-month visit.

Complications (Paper I and II): All in-hospital complications were recorded at the time of admission from the hospital. At the follow-up consultations, all adverse events that had occurred since the last visit were recorded. All subsequent surgical and medical interventions as well as readmission to the hospital or prolonged hospitalization were recorded as adverse events.

Definitions

Clinical failures (Paper I and II): Clinical failure was defined as persisting symptoms, worsening of symptoms or new symptoms with or without further treatment during the first six months after the initial treatment. In paper V, clinical failure during the first six months after treatment is referred to as "primary clinical failure" to avoid confusion with the term "clinical recurrence".

Clinical recurrence (Paper V): Clinical recurrence (or "symptom recurrence") was defined as new symptoms or worsening of symptoms that occurred more than 6 months after treatment, with or without repeated intervention.

Magnetic resonance imaging (MRI)

(Paper I, III, IV, V)

MRI examination of uterus and leiomyoma was performed before treatment in all patients. In the studies reported in paper I, II and V, the MRI examination was repeated after 1, 3 and 6 months. In the study reported in paper III and IV, MRI examination was reiterated the day after treatment and after 3 months. MRI studies were performed with a 1.5T Magnet

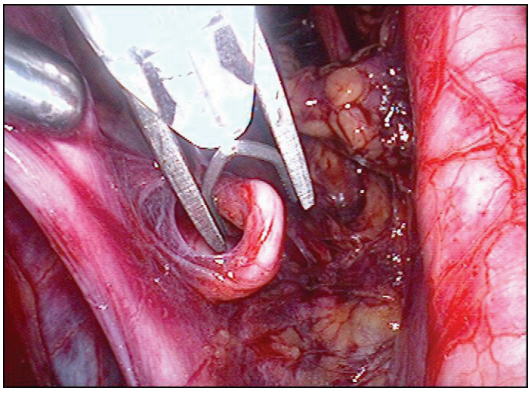
(Gyroscan NT Intera Philips, Best, The Netherlands). Using turbospin echo (TSE), T1-weighted pulse sequence images were obtained in the transverse plane. With the use of T2-weighted TSE sequences, imaging was performed in the transverse and the sagital plane. Transverse fast-field echo (FFE) images were acquired in optimal plane through the dominant leiomyoma after rapid intravenous administration of gadopentetate dimeglumine 0.1 mmol/kg/body weight (Magnevist, Schering AG, Berlin, Germany). Images were obtained every 5 seconds between 30 and 180 seconds after contrast injection. Finally, delayed TSE axial T1 images were obtained immediately after the FFE sequence. The total uterine volume and the volume of the largest leiomyoma were calculated from the sagittal and the transverse T2 images. The volume of the dominant leiomyoma and uterus were calculated using the formula for a prolate ellipsoid (Lenght×Width×Depth×0.5233), as described by Orsini et al. (70). Regions of interest (ROI) were placed in normal myometrium, middle of dominant leiomyoma, and the gluteus muscle. When leiomyoma was heterogeneous, the ROI was expanded to include a larger area. The T1 (and T2) properties of the leiomyomas were normalized using skeletal muscle for correction: T1=T1-leiomyoma/T1- skeletal muscle (184,235). The maximum enhancement index was calculated from the T1 images before and after contrast medium was given: [(T1 peak-T1 before)/T1before] x 100. The degree of infarction after treatment was estimated visually from the contrast enhancement images and categorized into complete infarction of all leiomyoma tissue with no enhancement, partial infarction with inhomogeneous or partial enhancement in one or some leiomyomas, and no infarction in any leiomyoma with unchanged enhancement from pretreatment examination. The number and location of leiomyomas > 2 cm were recorded. Submucous and subserous leiomyomas were classified according to a modification of the classification described by Wamsteker et al.(141). Pedunculated leiomyomas without intramural extension were classified as type 0 submucous or subserous leiomyomas, respectively. When the intramural part of the leiomyoma was less than 50%, the leiomyoma was classified as type I. With an intramural extension of 50% or more, the leiomyoma was classified as type II. If the leiomyoma had contact with both the endometrial cavity and serosa, it was classified as transmural. The term “transformation of uterus” was used in cases with multiple leiomyomas where there was difficult to find normal myometrial tissue or to define one single dominant leiomyoma. In paper V, we have used a simplified version of this classification with only leiomyomas type 0 and I presented as submucous or subserous.

5.5 Interventional Procedures

5.5.1 Laparoscopic bilateral occlusion of uterine arteries

(Paper I, II and V)

The patient was placed in the supine position without flexion of the hips. No cervical tenaculae was used. Under general anesthesia with tracheal intubations, a 10 mm trocar was inserted in the midline below the initial incision and two 5.5-mm trocars were inserted ipsilateral to the epigastric artery. The peritoneum between the round ligament and the infundibulopelvic ligament was incised with a scissor parallel to the external iliac artery. The retroperitoneal space was entered by blunt dissection. Atraumatic forceps were used to reach the lateral origin of the uterine artery. The obliterated umbilical artery was identified on the anterior abdominal wall. It was firmly grasped with a forceps and lifted to show its posterior part. Then the umbilical artery was dissected from the posterior location caudally towards its unobliterated part, that continuous into the internal iliac vessel. In this area, the origin of the uterine artery was found. Then the uterine artery was dissected towards the uterus to confirm that the artery was crossing over the ureter and then entering into the uterine wall. The uterine artery was occluded lateral to the ureter with one or two endoclip. In some cases, the internal hypogastric artery was occluded with a clip on one or both sides in addition to the occlusion of the uterine arteries. Finally, the utero-ovarial collateral arteries located in the utero-ovarial ligament were bilaterally coagulated using a bipolar forceps.



Clamping of the uterine artery.

(Photo by dr.Langebrekke, for illustration purposes only.The patient is not included in the study)

5.5.2 Uterine Artery Embolization

(Paper I, II and IV)

Unilateral right femoral artery was punctured and a sheath with inner diameter of 1.3 – 1.7 mm placed. The uterine arteries were intubated with a 65 cm long catheter with cobra curve. The catheter was gently placed using a soft and angled Teflon-coated wire. After placement the catheter was connected to a pressure transducer. If spasm was noticed by pressure drop or slow antegrade flow in the uterine artery 200 µg nitroglycerin and/or nifedipine 5 mg was injected intraarterially; if still spasm an 1 mm microcatheter was placed and the Cobra catheter pulled back into the hypogastric artery. The only diagnostic angiography performed was the ones to place the catheter into the right position. Both the uterine arteries were embolized with 355-500 µm polyvinyl alcohol particles (Contour, Boston scientific). The particles were mixed with contrast and nitroglycerin and injected slowly during fluoroscopy with 2-10 cc syringes until flow was nearly stopped. No further proximal occlusion with coils or gelfoam particles was performed.

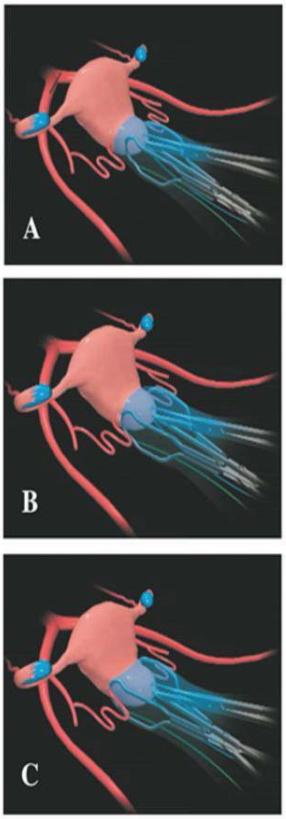
5.5.3 Temporary Doppler-directed transvaginal uterine artery occlusion

(Paper III and IV)

A prototype of the Doppler-directed, transvaginal uterine artery clamp system Flowstat® (Vascular Control Systems Inc, San Juan Capistrana, CA) was used. The system consists of a guiding cervical tenaculum, a transvaginal vascular clamp with integrated Doppler ultrasound crystals and a small battery powered transceiver that generated audible Doppler sound.
The uterine arteries were located by the use of the audible Doppler signals, and occluded with the vascular clamp.

The patients were placed in the lithotomy position in a standard gynecology treatment room. Nine patients were treated in paracervical blockage with addition of intravenously sedation while one patient was in general anesthesia when applying the clamp. The paracervical block was performed with injection of 20 ml bupivacaine (Marcain, AstraZenica, Oslo, Norway) at the 9:00 and 3:00 lateral cervical position, and a Schroeder tenaculum was applied to the cervix at the 6:00 cervical position.

The guiding tenaculum was placed in the 12:00 cervical position, and the Schroeder tenaculum was removed. The transvaginal clamp was attached to the guiding tenaculum. With help of the guiding tenaculum, the clamp was slid upwards along the vaginal mucosa close to the uterine body to the level of the vaginal fornices at the 9:00 and the 3:00 cervical position. When the clamp reached the uterine arteries, the crystals on the arms of the clamp return audible signals from the right and the left arteries.



The clamp was advanced further along the guiding tenaculum, displacing the uterine arteries superior to the point of insertion into the uterus. Then the clamp was closed. The absence of audible Doppler signals from the uterine arteries indicated that the uterine arteries were occluded bilaterally. The clamp remained in place for six hours.

Angiographic examination was performed with clamps in position. A 5F pigtail catheter was placed into abdominal aorta at the level of the renal arteries through right femoral artery puncture. Patency of the uterine arteries as well as collaterals through the ovarian arteries was evaluated. After the initial aortography we waited until the renal pelvis and the ureters were filled with contrast to evaluate for any obstruction of the ureters. When the uterine arteries were not occluded, the clamp was repositioned and the aortography repeated.

5.5.4 Preoperative preparation

Immediately prior to embolization and laparoscopy (paper I, II and V), one single dose of cefalotin 2 g (Keflin, Eli Lilly & Co, Indianapolis, Ind) and metronidazol 1.5 g (Flagyl, Aventis Pharma AS, Lysaker, Norway) as well as suppositories diclofenac 100 mg (Voltaren, Novartis Norge AS, Oslo, Norway) and paracetamol 800 mg + codeine phosphate (Paralgin Major, Weifa AS, Oslo, Norway) were given.

One hour prior to the vaginal clamping procedure (paper III and IV), one dose of rofecoxib 50 mg (Vioxx, MSD, New Jersey, US) per-orally and one dose of suppository paracetamol

500 mg (Paracet, Weifa AS, Oslo, Norway) were given. Just before treatment, the patients received one intramuscular injection of ketorolac 30 mg (Toradol, F. Hoffmann-La Roche Ltd, Basel, Switzerland).

5.6 Statistics

The data are presented as mean values for normal distributed data and as median values for skewed data. A two-sided t-test was used for comparisons of a continuous variable in two patient groups if the variable in question did not have a markedly skewed distribution. If the distribution was markedly skewed, a two-sided Wilcoxon-Mann-Whitney test was used. A paired t-test or Wilcoxon signed ranks test was used for comparison of paired data. A chi-square test or Fisher exact test was used when comparing categorical variables. The cumulative rates of recurrence and hysterectomy over time were calculated and compared using Kaplan- Meyer curves and the log-rank test. A significance level of 0.05 was used for all tests. For the papers I, II and V, we used the data program SPSS (SPSS Institute Inc., Chicago IL).

6. SUMMARY OF RESULTS

Paper I. Laparoscopic occlusion of uterine vessels for the treatment of symptomatic leiomyomas. Initial experience and comparison to uterine artery embolization

This prospective non-randomized study reported our initial experiences with 22 patients treated with laparoscopic bilateral occlusion of the uterine arteries and 24 patients treated with uterine artery embolization. The paper describes in detail the technique that we have used for both laparoscopic bilateral occlusion of the uterine arteries and uterine artery embolization in later studies included in this thesis. The treatment groups were not similar; the preoperative uterine size was larger and the body mass index was higher among patients treated with embolization compared to those treated with laparoscopy.

We found that all 22 laparoscopic procedures and 23 of the 24 embolization procedures could be successfully carried out. Due to bilaterally spasm in the uterine arteries, one of the embolization procedures could not be completed. After laparoscopic occlusion of the uterine arteries, the percentage reduction in PBAC scores at 1, 3 and 6 months were 37%, 52% and 50% respectively. After the embolization procedures, the percentage PBAC reductions at the same points were 64%, 63% and 67%. The volume of the dominant leiomyoma was reduced with 36% and the uterus volume was reduced with 37% 6 months after treatment with laparoscopy evaluated with MRI measurements. After UAE, the corresponding volume reductions were 45% and 40%. No comparisons between the treatments groups were performed for any of these variables. Pain registration by a visual analog score (VAS) scale was 1.4 cm after laparoscopy and 1.9 cm after embolization (P=0.40). The amount of opioid painkillers (ketobemidon) needed was significantly lower after laparoscopy with 16 mg compared to 38 mg after embolization (P<0.001). There were no peroperative complications in either of the treatment groups. Complications after laparoscopic occlusion of the uterine arteries occurred in 4 patients. There were one pulmonary embolus and 3 cases of temporary skin- and adductor muscle disturbances suspicious of affected obturator nerve. After embolization, four cases of post-embolization syndrome occurred; three with mild symptoms that resolved within 8 days, and one with more severe symptoms of relapsing fever and discharge. The latter one eventually accepted hysterectomy and a fistula between the appendix and the uterine cavity was found.

Secondary surgery was necessary in 5 additional patients. In the laparoscopy group one hysterectomy and one hysteroscopic resection of the endometrium was performed because of lack of effect of the primary treatment. In addition, one hysteroscopic resection was

performed because of expulsion of leiomyoma tissue. In the embolization group there were two cases of leiomyoma expulsion that resulted in hysteroscopic resection in one and dilatation and curettage in the other.

Paper II: Laparoscopic Occlusion Compared With Embolization of Uterine Vessels: A Randomized Controlled Trial

We randomized 66 patients to either embolization or bilateral laparoscopic occlusion of the uterine arteries. The clinical result 6 months after treatment was compared. Fifty-eight participants received treatment; 29 with embolization and 29 with laparoscopy. The primary endpoint – the percentage PBAC difference between pre-treatment and 6 month registration – did not differ between the groups, with mean 53% reduction after laparoscopy and 52% reduction after embolization. However, the 80% power of the study was only 52% to detect a difference in PBAC reduction of 20%. Bleeding reduction was reported among 25 patients (86%) after laparoscopy and among 26 patients (90%) after embolization (P=0.69) However, when differentiating the bleeding amount, significantly more patients complained about heavy menstrual bleeding 6 months after treatment in the group treated with laparoscopic occlusion of the uterine arteries compared to the group treated with embolization, 6 (21%) versus 1 (4%), (P=0.04). There were no other statistically significant differences regarding the symptom relieve between the two treatment groups. Clinical failure was seen in 6 (21%) subjects after laparoscopy and in two (7%) subjects after embolization (P=0.13).

Significantly less pain and nausea were observed after laparoscopy than after embolization during the first 48 hours after treatment. On a visual analog scale ranging from 0 to10, the maximum pain score was 3.7 after laparoscopy and 5.5 after embolization (P=0.010). The maximum nausea measured on the same scale was 2.8 and 5.4 respectively (P=0.007). Less use of ketobemidon was seen after laparoscopy (12 mg) compared to after embolization (46 mg), P<0.001. The duration of hospitalization varied significantly, with an average of 46 (24-72) hours after laparoscopy and 57 (24-108) hours after embolization (P=0.001). The median sick leave duration was 21 days after both treatments. Additional treatment was necessary in six patients (21%) after laparoscopy and in seven (24%) after embolization. Five subjects in the laparoscopy group and two in the uterine artery embolization group needed further treatment for persistent menorrhagia (P=0.42). Expulsion of leiomyoma necessitating secondary surgery occurred in one patient after laparoscopy and in five after embolization (P=0.19).

Vaginal discharge more than 10 days was experienced by four patients after laparoscopic occlusion compared to by ten patients after embolization, the difference was not significant. Serious complications occurred only in the laparoscopy group with one pulmonal embolism and two cases of temporary obturator nerve affections also reported in paper I. In addition, one woman had symptoms of claudication from the right buttock after bilateral occlusion of the hypogastric artery and was successfully treated with balloon angioplasty. Other complications were minor.

Paper III: Multiple Myomas Treated With a Temporary, Noninvasive, Doppler-Directed, Transvaginal Uterine Artery Clamp

This paper is a case report describing a successful treatment with a new device placed vaginally to temporarily occlude the uterine arteries. A 43 year-old woman with uterine leiomyomas and symptoms of menorrhagia, dysmenorrhoa and pelvic pain was treated with a vaginal clamp for 6 hours. MRI examination 3 months after treatment showed 49% reduction in uterus volume and 77% reduction in leiomyoma volume. The PBAC score decreased from 139 before treatment to 117 at three-month follow-up.

Paper IV: Treatment of Uterine Myomas with Transvaginal Uterine Artery Occlusion: Possibilities and Limitations

This experimental feasibility study included 10 patients. The uterine arteries were occluded bilaterally for 6 hours by the use of a vaginal clamp. During the occlusion, eight of the patients went through an angiographic examination. We found angiographic evidence of bilateral occlusion of the uterine arteries in 4 of the patients. One of these was excluded from further participation because of collateral blood-flow to the leiomyomas. The remaining three patients had reduced or no blood-flow to the leiomyomas the day after the procedure measured by contrast-enhanced MRI. Two of these three had remaining symptom control for 24 and 48 months with reduced menstrual bleeding measured by patients self-reporting and PBAC. The leiomyoma reduction was 87% and 39% measured by MRI 3 months after treatment. Two patients did not go through angiographic examination. One of these reported good clinical effect of the treatment, however slightly increased uterus volume was seen at 3-month MRI. She was followed for 12 months until menopause. The other one had increased uterus volume and still menorrhagia at 3-month control and went through uterine artery embolization 15 months after vaginal occlusion treatment. On

angiographic examination we found that two of the procedures occluded the ureter unilaterally. The hydroureter and hydronephrosis resolved itself within a week.

Paper V: Uterine artery embolization versus laparoscopic occlusion of uterine arteries for leiomyomas: Long term results of a randomized comparative trial

This is the long-term follow-up of the patients reported in paper II. In this study we compared the recurrence rate after UAE and LUAO. In addition, we investigated the MRI changes 6 months after treatment related to the two different treatments and the clinical outcome. Of the 58 patients who participated in the randomized study reported in paper II, 50 had no clinical failure at 6 months. This group of patients was followed for median 48 months (8-73) until hysterectomy or menopause. We surveyed the study participants annually about their leiomyoma related symptoms by outpatient visits, telephone or letter. In the initial study, all patients did go through MRI examination before intervention with either UAE or laparoscopic occlusion. Forty-eight of the fifty women with no primary failure at six months went through MRI examination at that time. We found a higher cumulative clinical recurrence rate after LUAO with 14 recurrences (48%) compared to after UAE with 5 recurrences (17%), log-rank test, P=0.02. The cumulative 5-year hysterectomy rate was also higher after laparoscopic treatment compared to after UAE, 8 (28%) versus 2 (7%), P=0.041. The MRI- measurements showed a significant larger uterus volume reduction with mean 51% after UAE compared to 33% reduction after laparoscopy (P=0.001). Contrast enhanced MRI examination revealed complete leiomyoma infarction in all patients treated with UAE and in only 5 patients treated with laparoscopy (P<0.001). Among 11 patients with recurrence, regardless of initial intervention, uterus volume was reduced with mean 24% compared to 48% in the 37 patients with no recurrence (P=0.004). Incomplete infarction of leiomyomas was seen in 73% (8/11 patients) in the recurrences group versus 24% (9/37 patients) in the non-recurrence group (P=0.009).

7. GENERAL DISCUSSION

7.1 Patient selection

All patients included in the studies were recruited among patients referred from their private gynecologist or general practitioner to the university clinic because of symptoms of uterine leiomyomas requiring therapy. Some of the patients in paper I were allocated to a specific treatment based on uterine size, since all patients with a uterine size exceeding the umbilical level were assigned to embolization treatment. The baseline characteristics of the patients in that study were also otherwise different, e.g. the body mass index was different between the two treatment groups. This implies that the two treatment groups were not completely comparable.

However, the primary purpose of the study reported in paper I was to explore the uterine artery occlusion method in a pilot study and to investigate if it was possible to compare the two treatment modalities in a randomized study later. The patients reported in this paper are a mix of the first 10 patients in a non-randomized pilot study (5 patients in each treatment group), 9 patients that did not want to participate in a randomized trial or by whom the uterus was too large according to the eligibility criteria, and the first 27 randomized patients that were treated. In this first study, because of the diversity of the patients participating, we chose not to perform statistical analyses to compare the two treatment groups with regard to the main outcome variables. We realize, however, that it might be questioned that we used data from some of the randomized patients reported in paper II together with the other non-randomized participants from paper I.

7.2 Methodological considerations

7.2.1 Sample size and power calculation

The primary endpoint that was chosen for the randomized study presented in paper II was the percent reduction in menstrual bleeding 6 months after treatment measured by pictorial blood loss assessment chart. The sample size was calculated under the assumption that a 20% difference in pictorial blood loss assessment chart score between the groups would be of clinical significance. Based on a standard deviation of 27 for the percentage change in PBAC, 30 patients were needed for each treatment group to define a statistically significant difference with a power of 80%. Sixty-six patients were enrolled to take allowance for a

drop out rate of 10%. The standard deviation for the percentage change in PBAC score was chosen based on one of the authors (OI) earlier studies of PBAC changes after transcervical resection (non-published data). However, when calculating the percentage change in PBAC score in this study, the actual standard deviation was found to be 37. Thus, the power of the study with respect to the PBAC difference was only 52%. Due to the low power of the study, definite conclusions regarding the main efficacy variable (PBAC reduction) could not be drawn. With the actual standard deviation, it might be shown that a sample size of 110 patients is necessary to detect a difference of 20% for this variable.

7.2.2 Inclusion period

Patients in the randomized study were included between December 2000 and December 2004. The first patient was treated at the end of December 2000 and the last patient was treated in April 2005. This is a long inclusion period due to difficulties in finding patients willing to undergo randomization between two treatments. In addition, the study was stopped for 6 months between April and October 2003 because of a serious event after one embolization procedure. One patient, not included in any of the presented studies, was admitted to the department 5 days after uterine artery embolization with signs of bowel perforation. She went through an emergency operation, but unfortunately died in septical shock 7 days after the initial treatment. All uterine artery intervention treatments were stopped until medical and legal investigations were finished. Finally, the investigations concluded with bowel perforation because of a malignant tumor in the colon sigmoid not associated with the embolization treatment, and the study was allowed to restart.
The long inclusion period could possibly have biased the randomized study. There might have been differences in the referral policy, in the patient population or in the treatment and nursing offered in the department. These factors have to some extent been neutralized by the nature of the randomized design of the study. The protocol was not changed during the study, and there was no change in the technique or instruments used for the interventions neither during the embolization nor during the laparoscopic procedures. However, there might have been some differences in the way the general anesthesia was performed during the laparoscopic procedures since the anesthesiologists changed during the study period. In addition, the MR images were digitalized during the time of the trial. One radiologist (ABB) that took part in the evaluation of the MRI examinations in the start of the study started to work in another hospital and did not continue as investigator after paper I was published;

however, all other investigators both in the gynecological and the radiological department remained constant during the study period.

7.2.3 Randomization

The manual method that we used for randomization might be questioned. Concerns have previously been expressed about violation of the random principle during assignment to treatment by use of sealed envelopes during the randomization procedure (236). The alternative would be to use a random number generator either from tables or by use of a computer program to complete the randomization within the blocks. However, these services are expensive and were not available at the hospital when the study was performed.

7.2.4 Implications of a non-blinded design

Since none of the studies were blinded, the registrations of the patient's subjective symptoms, the satisfaction, the postoperative pain and nausea, the duration of hospital stay as well as the number of additional interventions might have been biased. One of the investigators (KH) that also performed the laparoscopical procedures did look after most of the patients during the hospital stay as well as she saw the majority of the patients for the controls. This might have influenced these variables.
Also the evaluation of the MR images could have been influenced by the readers. All MR images were initially read by radiologist with experience in gynecological radiology. After the six-month follow up, all examinations were reviewed by one of the two radiologists (HJN, NEK). One of them (NEK) performed most of the uterine artery embolization procedures. Both were blinded to the included groups, but quite early it was obvious to the observers which group the patient belonged to from the contrast enhanced images.

7.2.5 Strength of the study

It is generally accepted that new treatments should be evaluated in randomized controlled trials. However, many new surgical modalities are implemented without comparative studies. This thesis present the first randomized study of laparoscopic occlusion of uterine arteries compared to uterine artery embolization.

7.2.6 Outcome measures

PBAC measurements

PBAC is a semi-subjective outcome measure, depending partly on the women's own perception of blood-loss. The exact amount of blood-loss is not measured. The discriminatory power of the PBAC as a diagnostic test for menorrhagia has previously been questioned (237). However, it is demonstrated that the method is superior to a woman's full subjective perception and assessment of menstrual blood loss without a chart, even if PBAC is performed only once, and the consistency when women assess a second period appears to be high (238). Discrimination between menorrhagia and normal menstruation was not intended in our study. The treatment was decided based on the women's own perception of symptoms, which also is how menorrhagia usually is managed in clinical practice (72).
A more accurate method to measure the periodic blood-flow would be the alkaline hematin method, which is commonly used as the golden standard for this purpose. The method involves, however, considerable inconvenience both for the patient and the doctor, since the patient have to collect all her used sanitary pads and tampons and bring them with her to the doctor, which in turn have to extract the blood for analyses. The use of this method to estimate the periodic blood-loss would most likely have reduced the response and compliance in the study. The Society of Interventional Radiology (SIR) recommends the use of PBAC measurements in scientific reports involving uterine artery embolization (239). The original validation of pictorial blood loss assessment chart (240) was performed using standardized sanitary pads and tampons. Women in our study used their own regular sanitary pads and tampons and this could possibly have generated bias in the results. To reduce this bias, the women were encouraged to use the same brands and sizes of pads or tampons throughout the study period. In addition, only the percentage reduction in pictorial blood loss assessment chart for each subject was used in the analyses.

Evaluation of pain, nausea and the amount of ketobemidon used

We tried to minimize the possible bias connected to these measurements by the use of a fixed painkilling regime as the basis medication and with additional narcotics (ketobemidon) that was patient-controlled. However, because of the marked differences in the nature of the interventions, that required general anesthesia in one (laparoscopy) and only local anesthesia in the other (embolization), the total amount of painkilling medication did vary between the groups and also within different patients within the same group. To be more certain to have eliminated the effect of medicaments given during the interventions, it

might have been better to measure the pain, nausea and ketobemidon used the day after the procedure.

MRI-examinations

The protocol included MRI examinations at 1, 3 and 6 months after the study intervention procedures. Only the 6-month measurements are used in the analyses because those were the most complete ones. There were a considerable number of missing or incomplete examinations at 1 and 3 month-examination. Together with the limited number of patients studied, we found that these result would be difficult to evaluate.

During the study two improvements took place which affected evaluation of the MRI. The digital storage system, the PACS, was implemented in the department and thereby stored the MRI pictures. The digitalized images made it easier to review the images. Also, at the time we started we were only able to scan the uterus with three slices during contrast enhancement imaging. It was therefore possible to miss some of the myomas at follow-up. These changes took place after the first 15 study-participants had been through MRI examination. This implicates that the earliest MRI evaluations are less reliable than the later ones.

The calculations of uterus and leiomyoma volume were performed by the use of three perpendicular diameters incorporated in the equation of an ellipsoid. The accuracy of uterus volume assessment by use of the ellipsoid formula based calculation has been evaluated against the parallel planimetric MRI method as a standard. The investigators found that the ellipsoid formula based calculation has excellent performance and is considerable less time-consuming, and is therefore to be preferred in studies evaluating treatment of uterine leiomyomas (235).

Follicle Stimulating Hormone (FSH) measurement

FSH was taken before and after treatment. After publication of paper I, we did not use these measurements further in our analyses. We realized that the FSH would spontaneously vary considerable in the age group of patients in our studies. In addition, the FSH value varies considerably during the menstruation cycle (241). To obtain a standardized parameter for ovarian reserve, the blood-samples must be collected at the 3rd day in the cycle (242). This standardization was difficult to obtain in our patient group, partly because of patient compliance, irregularity in the cycles and sometimes permanent vaginal bleeding, especially prior to the interventions. To obtain a more reliable measurement of the patients hormonal

status and the ovarian reserve reduction after treatment, one could have used the cycle-independent anti-Müllarian-hormone (AMH) (243,244). After consideration, we decided to use only the clinical evaluation (amenorrhoea) as a parameter on menopause.

7.2.7 The intervention procedures

Laparoscopic occlusion technique

According to the protocol, the utero-ovarial anastomotic sites were coagulated in addition to division of the uterine arteries in order to avoid collateral perfusion to leiomyomas. When we started to perform the procedure, we used the technique originally described by Liu et al. (217), that included coagulation of the utero-ovarian ligament. As described in the introduction chapter, angiographic studies have visualized flow from the ovaries to the uterine artery and leiomyomas in about 25% of patients (57). This additional procedure during surgery might possibly have increased the risk of ovarian failure, since the blood-supply to the ovaries is found solely from the uterine artery in 4-6% of women (57,60). Holub et al. compared LUAO with and without coagulation of the utero-ovarian anastomoses in a non-randomized, prospective study of 90 patients with a mean follow-up of 16 months. The authors did not find any statistically significant differences with regard to symptom reduction, leiomyoma reduction or subsequent interventions between the groups of patients. However 6 (9%) secondary surgeries were performed in the group of 67 patients without anastomoses occlusion compared to none in the group where the anastomoses sites were closed. The authors report normal FSH levels in all patients 3 months after treatment and no patients with menopausal symptoms (245).

Uterine Artery Embolization

During the embolization procedure, the field size was limited in order to reduce the radiation exposure. Thus, we have no information of the presence or not of ovarian collaterals.

Controversies exist about the choice of particles during the embolization procedure. Our protocol for uterine artery embolization included the use of PVA particles. Those were the first embolic agents used for UAE (151,246) and long-term results are good (165,166). Spherical embolization particles such as TAGM have been developed for use in the neuroradiological field, in which calibration of the embolization agent is crucial. A better

distribution of TAGM compared to non-spherical agents like PVA has been observed in animal models (247). It is argued that the irregular shape and large granulometric size range of the conventional PVA particles result in more clumping and less predictable level of arterial occlusion compared to the calibrated TAGM (247,248). Because embolization of the uterine arteries is based on the preferable flow to the leiomyomas, it is important to avoid spasm (249). Microcatheters are often used to avoid this, and Spies et al. found that nonspherical PVA particles were more likely to cause obstruction in these catheters compared to spherical TAGM (250).
We have not used microcatheters routinely, but 4-F catheters. To avoid spasm, the PVA-particles were mixed with nitroglycerin. Still, if spasm occurred, injection of nitroglycerine and/or nifedipine or microcatheter was used.
It is claimed that small nonspherical PVA particles contra calibrated spheres would affect normal myometrium more extensively and cause more post procedure pain (251). Studies comparing the use of the two different agents could not support this theory (252,253).

Another issue discussed among interventional radiologists is which angiographic endpoint to use in order to achieve devascularization of the leiomyomas without unnecessary damage to the myometrium ("overembolization"). With the use of TAGM for uterine artery embolization, a limited embolization technique was introduced. This technique uses the angiographic endpoint described as "near-stasis" with the common uterine artery still patent and all distal portions occluded (249). The limited embolization protocol is thought to reduce the necrosis in the myometrium and cause less pain and discomfort for the patients. However, no studies have confirmed this theory.
The treatment protocol at the time the study presented in this thesis was started described the established method with the angiographic endpoint "stasis" or "near-stasis" and reflux of contrast medium towards the uterine artery origin. With the importance of maintaining constancy during the study in mind, we did not find evidence that justified a change in the technique or in the embolic agent used during the study period.

Temporary Doppler-directed transvaginal clamp

The manufacturer of the clamp has changed since the study was performed. The new manufacturer has made small changes to the design of the clamp: The shape on the tip of the clamp is modified to perform a better and more reliable grip on the tissue.

7.2.8 Statistics

Intention to treat/ per protocol analyses

In paper II, we analyzed the result both according to the principle of intention to treat and per protocol. However, we excluded the patients that were randomized, but did not receive any of the interventions, from all our analyses including the intention to treat analyses. According to Fergusson et al. post-randomization exclusion will not bias the result of intention to treat analyzes in cases of premature randomization and for patients that do not meet the eligibility criteria if they never received the intervention (254). This is the case for the eight patients in question and we found it reasonable to exclude them.

Missing values

Six patients had missing PBAC scores in the analyses in paper II, two in the embolization group and four in the laparoscopy group. Since the reduction in PBAC was set to zero in these cases, according to the intention to treat principle, there might have been slightly better results regarding this variable in the laparoscopy group if all values had been present.

7.3 Interpretation of the result

Paper I, II and V

Paper I, II and V report the results of treatment with laparoscopic occlusion of the uterine arteries and uterine artery embolization. The first study (paper I) confirmed the feasibility of both treatments in our hospital. We found significantly reduced leiomyoma and uterus volumes measured by MRI, as well as reduced menstrual bleeding, measured by PBAC after both treatment modalities compared to before treatment. The laparoscopic procedure involved significantly less need for narcotic painkillers. This was confirmed in the next study (paper II) in which the patients were allocated to the two treatment groups by randomization. In addition, significantly more pain and nausea was found in the randomized study. The finding of shorter hospital stay after laparoscopy compared to after embolization (paper II) supported this result, although the recovery time after treatment was not shown to be different. We thought that the smaller amount of pain after laparoscopic occlusion could be partly due to more collateral vascular supply to the uterus compared to after embolization. When analyzing the MR images (paper V) six months after treatment, we

We did not compare the PBAC-reduction in the first non-randomized trial (paper I). In study number two (paper II), the patients were allocated to the two different treatments by randomization, and the percentage PBAC reduction 6 months after treatment was used as the primary endpoint. There was no difference between the study groups when comparing this variable. Unfortunately, as discussed above, the study reported in paper II was underpowered with regard to the PBAC measurement, and thus we could not draw any conclusion regarding the most effective treatment based on this variable.
However, significantly more patients did complain of heavy bleeding six months after treatment. The latter variable is an even more subjective assessment than PBAC, and very weakly correlated to the actual amount of bleeding (255). According to Warner et al., the perception of heavy bleeding could still be of value since it probably takes into account more than the total blood volume. This could be difficulties with the containment of blood flow and associated symptoms or acute unmanageable blood flow in the first few days (72). We did see that in three patients who still complained of heavy bleeding after six month, which was not classified as primary clinical failure because of improvement of symptoms and initially no need for subsequent treatment, recurrence occurred with extended follow-up (paper V).

At 6 months after treatment (paper II), we found a tendency of more clinical failures after laparoscopic occlusion of the uterine arteries, with 6 cases compared to 2 cases after embolization, but the finding was not statistically significant. The lack of significance with regard to this numbers might have been caused by the low number of participants studied. When analyzing the long-term follow up of the patients (paper V), the cumulative recurrence rate was found significantly higher after treatment with laparoscopic occlusion compared to after embolization, which may lead to the assumption that also the difference in primary failures would have been statistically significant with an appropriate sample size. The 6-month MRI-results reported in paper V revealed significantly less infarcted leiomyomas in the group of patients treated with laparoscopy compared to the group treated with embolization. It is possible that a larger study with a sufficient sample size also would have showed minor or no difference in the short time result after the two treatments, and that the higher recurrence rate after laparoscopy reported in paper V is due to

revascularization of the leiomyomas after a period of time. Several authors have stated that incomplete infarcted leiomyomas will have the ability to regrow and cause recurrence of symptoms with time (190,191). Kroencke et al., however, studied two different embolization protocols and proposed that incomplete infarcted leiomyomas that was seen at MRI examinations 24-72 hours after embolization did cause early failure and repeat interventions already after 3 months follow-up, although the number of patients in their study was small and no statistical analyses were given (189). Contrast-enhanced MRI examination early after the treatments would perhaps have given us more information aimed to discuss these mechanisms.

The complications reported in paper I and II after both laparoscopy and embolization are of importance. The case of pulmonal embolism that occurred one week after laparoscopy was probably induced by surgery. The patient had no known increased risk of thromboembolism before treatment. The alternative option for the patient would have been embolization or hysterectomy, which both carries the risk of thromboembolism (256-258). We do not think that we exposed the patient to a greater risk by offering her the laparoscopic treatment. The temporary obturator nerve affections that were seen in three patients (paper I and II) occurred in the beginning of the study. We think that this complication was due to our lack of experience with the surgical procedure and that either a hematoma or too rough manipulation of the nerve caused this unfortunate problem for the patients. The same complication is also reported by one other author after difficult dissection in relation to an absent uterine artery (222). Claudication of the gluteal muscle as a result of hypogastric occlusion was unexpected (paper II), usually there are enough collaterals for a sufficient blood supply to the pelvis after closing the hypogastric artery (259). This complication illustrates the diversity of the functional pelvic vascular anatomy and the importance of carefulness when surgery is performed in this area.
After uterine artery embolization, there were 5 patients with prolonged fever and pain, diagnosed as postembolization syndrome (paper I and II). This is expected when compared with other studies (151,153). One of these patients needed a hysterectomy. A necrotic uterus and a fistula between appendix and the uterus were found during surgery. Total necrosis of the uterus is a rare, however known, complication to both embolization and laparoscopic occlusion of the uterine arteries (222,260).
Expulsion of leiomyomas is well recognized after uterine artery embolization (152,246,261). It is discussed in the literature whether this occurrence should be regarded as

a complication (174,262) or not. Some authors do not recommend performing uterine artery embolization in patients with submucous leiomyomas because of the assumed risk of expulsion and subsequent surgery (263). Others see the advantage of faster and more complete restoration of the uterus (174,264).We included all submucous leiomyomas that were not suitable for hysteroscopic resection. This resulted in 6 (21%) leiomyomas with submucous location in each treatment group. Thus, the relatively high number of subsequent interventions indicated by leiomyoma expulsion reported in paper I and II, may be caused by our selection of patients.
Menopause occurred only in women older than 45 years during the study period. However, we have not evaluated the ovarian reserve after the two treatments. Clearly, both treatments might have carried risk of ovarian damage because of the techniques used. In patients treated with laparoscopic occlusion of the uterine arteries, the additional coagulation of the utero-ovarian collaterals may have reduced blood-flow to the ovaries. In those treated with UAE, risk of non-target embolization of ovarian collaterals existed.

In addition to the difference that we found between the groups with regard to the degree of infarction of the leiomyomas, there was also significantly less volume reduction of the uterus in the group treated with laparoscopy compared to the group treated with embolization (paper V). Also when comparing the groups with recurrence and those without, regardless of treatment, and when comparing the patients with and without recurrence in the laparoscopy group, we found the same result. Although the sample size was too small to perform analyses to adjust for other variables (265), our findings support previous statements about the association between recurrence and both smaller post-treatment volume reduction and incomplete infarcted leiomyomas (165,266).

Less favorable results after laparoscopy with regard to recurrence of symptoms, less infarcted leiomyomas and less reduction of uterus volume could be explained by technical surgical failure as discussed in paper V. Two authors have reported less recurrence after laparoscopic occlusion of the uterine arteries than we have found. Holub et al. reported 9% recurrences in 114 patients 24 months after treatment (222). Wang et al. followed the patients for 48 months and reported 27 (28%) recurrences in 95 patients treated with laparoscopic occlusion (223). The preoperative volumes of the uterus and leiomyomas are not given in any of these studies, which make the selection of patients difficult to compare. The surgical procedure in our patients was sometimes challenging with large uteri and

restricted view. The relatively high number of surgery related complications might reflect this. We have evidence of one surgical failure because of insufficient occlusion of the uterine artery on one side. This patient experienced recurrence of symptoms and went through angiographic examination as preparation for uterine artery embolization as secondary treatment (paper II). Since the protocol did not include angiographic examination after surgery, we do not know if there are more similar failures.
Another possible reason for the poorer results after the laparoscopic treatment may be the more proximal occlusion of the uterine artery and less injury to the distal smaller vessels compared to what the particles during the embolization procedure causes. This could leave a greater amount of collaterals left open or with better ability to expand.

Paper III and IV

Paper III and IV report the experimental feasibility study of the transvaginal temporary vascular clamp. The case reported in paper III demonstrated that it was possible to achieve effect of the treatment on symptoms with short follow-up, and the MRI measurements confirmed devascularization and reduction in leiomyoma volume. However, this was only a case-report and could not tell us anything about how many patients that would benefit from the treatment. The more distal occlusion of the uterine arteries provided by the clamp compared to what was the case during the laparoscopic occlusion could theoretically result in more favorable effect with the clamp treatment. On the other hand, uncertainty exists with regard to the necessary duration of the occlusion. The rationale for the 6-hours duration of the clamp is as described in the introduction, the time needed for the myometrium to reperfuse after permanent occlusion of the uterine arteries by laparoscopy (233). There are no studies that evaluate the effect of occlusion in different periods of time.
In paper IV, the difficulties of applying the clamp correctly without affecting the ureters were demonstrated. In addition, the visualization of collateral supply from the ovary in one patient illustrated one limitation of this treatment modality, although the small number of patients studied prevents us from any estimations of how many patients this would affect. We think that one of the reasons for the difficulties of applying the clamp correctly was large leiomyomas that involved the isthmus or cervical area, and thus modulating the course of the uterine artery. However, even with a different selection of patients and successful technique, there will be the issue of collaterals, in particular, the utero-ovarian anastomoses and small existing collaterals that may expand and reduce the success rate even with a perfect application of the clamp. On the other hand, when compared to laparoscopic

permanent occlusion of the uterine arteries, where similar limitations exists, the transvaginal temporary placed clamp provides a much less invasive modality of treatment that, even with a lower successes-rate compared to embolization of the uterine arteries, could be attractive to some patients.

8. CONCLUSION

We found that laparoscopic permanent occlusion of the uterine arteries had effect on symptoms caused by uterine leiomyomas on short-term follow up in the majority of patients. The treatment also induced shrinkage of leiomyomas and uterus size measured by MRI 6 months after treatment in most patients. However, the risk of recurrence appears to be high: We found a 48% cumulative 5-year recurrence-rate in our study. In addition, surgery-related complications were significant.

The comparison to uterine artery embolization in a randomized study showed no difference in outcome 6 months after treatment measured with PBAC reduction as the main outcome variable. However, the study was underpowered with regard to this variable, and no definite conclusions could be drawn. Comparison of 6-month MRI results revealed larger number of patients with complete infarcted leiomyomas and more shrinkage of the uterus size after uterine artery embolization compared to after laparoscopic occlusion of the uterine vessels. The long-term follow-up of the same study showed a significantly better clinical outcome after embolization with 5 (17%) clinical recurrence compared to 14 (48%) recurrence after laparoscopy. Hysterectomies were also significantly fewer after embolization, and were necessary in 2 (7%) patients compared to 8 (28%) after laparoscopy.

Analyses of the MRI results after both embolization and laparoscopic occlusion of the uterine arteries supported the notion that incomplete infarcted leiomyomas and smaller post-treatment volume reductions are associated with higher recurrence rates.

In the experimental study of a temporary, noninvasive Doppler-directed, transvaginal clamp aimed to treat symptomatic uterine leiomyomas there were technical difficulties with regard to applying the clamp correctly. We were only able to confirm the correct placement of the clamp in half of the patients by angiographic examination. We found some indication of treatment effect on contrast-enhanced MRI examination the day after the procedure and one patient had also good clinical effect up to 24 months after treatment. The risk of occluding the ureter during the application of the clamp was confirmed by the angiographic examination. The efficacy and safety of the clamp needs further evaluation.

9. RECOMMENDATIONS

Based on our studies, we would recommend uterine artery embolization instead of laparoscopic occlusion of uterine arteries to most women with symptoms caused by uterine leiomyomas where hysterectomy or myomectomy is not the option.

Laparoscopic occlusion of uterine arteries may be evaluated in further studies as an additional procedure during surgery aimed at reducing intra-operative blood-loss and recurrence rate after myomectomy.
With the aim to avoid unnecessary surgical complications, such studies should be performed only by skilled surgeons with experience in laparoscopic retroperitoneal dissection. In addition, we would recommend not occluding the utero-ovarian collaterals unless after appropriate counseling about the risk of ovarian damage.

Contrast-enhanced MRI is a useful tool to evaluate the effect of vascular interventional treatment. However, the examination implicates considerable costs and is time-consuming and sometimes inconvenient for the patients. Simpler and less expensive methods such as color-Doppler ultrasound should be evaluated as an alternative tool.

Patients with submucous leiomyomas that are treated with vascular interventional methods should be informed about the risk of leiomyoma expulsion and subsequent surgery.

The temporary, Doppler-directed transvaginal uterine artery clamp needs further evaluation to clarify the efficacy and safety.

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11. CORRECTIONS

Paper I.

Abstract, page 37: “Postoperative pain and use of pain relief differed significantly,” should be: “Postoperative use of pain relief differed significantly,”

Abstract, page 37: P = .008, should be: P = .00

Material and methods, page 38: “The patients were followed at the outpatient clinic with visits scheduled at 6 weeks, 3 and 6 months after the operation”, should be “The patients were followed at the outpatient clinic with visits scheduled at **4** weeks, 3 and 6 months after the operation.”

Material and methods, page 38: Uterine bleeding was quantified by the semiquantitative pictorial blood loss assessment score (PBAC), completed by all subjects over a screening period of 2 months before enrolment, should be “Uterine bleeding was quantified by the semiquantitative pictorial blood loss assessment score (PBAC), completed by all subjects during one menstrual period before enrolment.”

I

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II

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III

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IV

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Appendix

S = liten klump

B = stor klump

MENSTRUASJONSBLØDNING: INSTRUKSER

1. Skriv ned den første datoen (den første dagen av Deres menstruasjon).
2. Sjekk bindet på begge sider og sammenlign Deres bind eller tampong med tegningene i tabellen, før De kaster det.
3. For å kunne registrere blødningen, tegn en strek (|) i den ruten i tabellen som ligner på Deres bind/tampong. Gjør dette hver dag av menstruasjonen.
4. Når De har fire streker (||||), tegn den femte streken slik: (𝍸).
5. Dersom De ser en klump på Deres bind/tampong eller De ser en i toalettet, merk Dem størrelsen og antallet hver dag. Beregn størrelsen ved å sammenligne med eksemplene ovenfor.
6. Dersom De har sterk blødning, skriv en F i ruten som korresponderer med den dagen det skjedde.
7. Hvis De ikke blør eller det ikke er tilstrekkelig blødning til å bruke beskyttelse, vennligst skriv "ingen blødning" i tabellen.
8. Glem ikke å ta med tabellen(e) til Deres gynekolog ved det neste kliniske besøket. Dersom De ikke forstår hvordan De fyller ut disse tabellene, spør Deres gynekolog. Det er viktig at de fylles ut korrekt.

EKSEMPEL

	DAG AV MENSTRUASJON							
BIND	1	2	3	4	5	6	7	8
	||	|	|	|||	||	|		
		||	𝍸 ||	|||	|			
		||	|					

	DAG AV MENSTRUASJON							
	1	2	3	4	5	6	7	8
KLUMPER		S x 2 B x 1	B x 1					
STERK BLØDNING		F						

På den 2. dagen i eksemplet ovenfor, viste ett bind lett blødning, to bind moderat blødning og to viste stor blødning. På denne dagen var det også to små blodklumper, en stor blodklump og et tilfelle av meget sterk blødning.

DERES MENSTRUASJONSBLØDNING

DATO SOM KORRESPONDERER MED DEN FØRSTE DAGEN AV DERES MENSTRUASJON

dag _____ *måned* _____ *år* _____

	DAG AV MENSTRUASJON							
BIND	1	2	3	4	5	6	7	8
								
								
								

	DAG AV MENSTRUASJON							
TAMPONG	1	2	3	4	5	6	7	8
								
								
								

	DAG AV MENSTRUASJON							
	1	2	3	4	5	6	7	8
KLUMPER								
STERK BLØDNING								

Pictorial Blood loss Assessment Chart, Norwegian version